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Research Article

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Research Article

Albumin influences leucocyte FcRn expression in the early days of kidney transplantation

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Abstract

FcRn, a receptor originally known for its involvement in IgG and albumin transcytosis and recycling, is also important in the establishment of the innate and adaptive immune response. Dysregulation of the immune response has been associated with variations in FcRn expression, as observed in cancer. Recently, a link between autophagy and FcRn expression has been demonstrated. Knowing that autophagy is strongly involved in the development of reperfusion injury in kidney transplantation and that albuminemia is transiently decreased in the first 2 weeks after transplantation, we investigated variations in FcRn expression after kidney transplantation. We monitored FcRn levels by flow cytometry in leukocytes from 25 renal transplant patients and considered parameters such as albumin concentrations, estimated glomerular filtration rate, serum creatinine, serum IgG levels, and ischaemia/reperfusion time. Two groups of patients could be distinguished according to their increased or non-increased FcRn expression levels between days 2 and 6 (d2–d6) post-transplantation. Leukocyte FcRn expression at d2–d6 was correlated with albumin concentrations at d0–d2. These results suggest that albumin concentrations at d0–d2 influence FcRn expression at d2–d6, raising new questions about the mechanisms underlying these original observations.

Keywords: FcRn, albumin, kidney transplantation, flow cytometry

Introduction

FcRn, the neonatal Fc receptor for immunoglobulin G (IgG), was initially studied for its role in the feto-maternal transmission of IgG [1]. It is composed of an alpha heavy chain non-covalently associated with beta-2-microglobulin, and belongs to the major histocompatibility complex class I family [2–4]. FcRn is ubiquitously expressed in the organism throughout life and is mainly located in intracellular endosomes in a wide number of cell types including epithelial, endothelial, or haematopoietic cells [5]. Its expression is regulated by DNA methylation of its *FCGRT* gene [6], *FCGRT* polymorphisms [7], miRNA [8], and transcription factors [9–11]. The latter are responsible for tumour necrosis factor (TNF)-α-induced FcRn upregulation *via* the NF-κB pathway, or interferon (IFN)-γ-dependent FcRn downregulation *via* JAK/STAT1 signalling [9, 10].

IgG and albumin, the most abundant proteins in the circulation, are the two major ligands of FcRn [12, 13]. FcRn is involved in their recycling and extension of their lifespan as well as their transcytosis across cellular barriers and their biodistribution in the organism [5, 14]. These processes require FcRn binding to its ligands in a pH-dependent manner, i.e. with high affinity at acidic pH (~6.5) and no binding at physiological pH [15]. FcRn participates in physiological processes such as feto-maternal passive transfer of immunity [1, 16], IgG transcytosis between the intestinal lumen and mucosa-associated lymphoid tissue [17]. FcRn is also involved in renal reabsorption by proximal tubule epithelial cells of albumin and IgG which pass through the glomerular filter by transcytosis [18–21]. Finally, FcRn regulates innate and adaptive immunity through the processing and presentation of immune complexes [22, 23].

In pathology, the involvement of FcRn in cancer is now well recognized [24–26]. Its expression is downregulated in cancer cells as well as in the tumour microenvironment. Low level of FcRn has been associated with poor patient survival in non-small cell lung cancer [27]. FcRn has also been implicated in autoimmunity [28], although many studies are still currently ongoing to clarify how it contributes to the dysregulation of the immune response [29–31]. We have recently described variations in FcRn expression levels within leukocytes in patients with systemic lupus erythematosus [32].

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Knowledge of the regulatory parameters of FcRn expression is increasing rapidly. Recently, a link between autophagy and FcRn expression has been demonstrated [33, 34]. Knowing that this phenomenon is strongly involved in the development of reperfusion injury in kidney transplantation [35–38], and also that albuminemia transiently decreases in the first 2 weeks after transplantation [39], we decided to evaluate variations in FcRn expression after kidney transplantation. To investigate this point, we monitored a cohort of renal transplant patients for FcRn expression levels in leukocytes during the first 2 weeks after transplantation, and considering parameters such as albumin concentrations, estimated glomerular filtration rate (eGFR), serum creatinine, serum IgG levels, and ischaemia/reperfusion time.

Materials and methods

Blood collection

Venous blood collected on EDTA (ethylenediaminetetraacetic acid) was obtained from 20 healthy donors from the 'Etablissements Français du Sang' (agreement N°CA-REC-2019-188). Blood samples from renal transplant patients at the Tours Regional University Hospital Center were obtained from routine biological analyses (lymphocyte phenotyping or blood cell count), when a biological analysis was prescribed. Clinical and biological data of patients were included in the ASTRE database agreement number: DR-2012-518.

Flow cytometry assay

Three hundred microlitres of blood were washed twice with phosphate-buffered saline containing 2 mM EDTA and 2% of foetal bovine serum by centrifugation. One hundred microlitres of cell pellet were stained with an anti-CD45 (Krome Orange, Beckman Coulter), 15 min on ice. Then, 2 mL of VersaLyse (Beckman Coulter) was added and incubated for 15 min at room temperature. After centrifugation, two fixation steps were performed: one with 150 µL paraformaldehyde (PFA 4%), followed by a second one with 150 µL of FlowX FoxP3/Transcription Factor Fixation (R&D System). FcRn staining was carried out with 50 µL of anti-FcRn (clone #937508, FITC, R&D System) diluted 1:100 in permeabilization buffer (Perm Buffer, R&D System) or 50 µL isotype control in the same buffer, 30 min on ice in the dark.

Acquisition was performed using a Navios cytometer (Beckman Coulter) and the data were analysed with Kaluza version 2.1 software (Beckman Coulter). FcRn levels are expressed as the ratio of anti-FcRn to isotype mean fluorescence intensity (MFI).

Measurement of serum creatinine, albumin, and IgG

Serum creatinine, albumin, and IgG were determined on serum samples using the COBAS 6000 analyser® (Roche Diagnostics, Meylan, France). The estimated glomerular filtration rate was determined using the CKD-EPI formula.

Statistical methods

Statistical analysis was performed with GraphPad Prism™ 9.0 software. Comparisons between two groups of patients (increased FcRn expression vs. non-increased FcRn expression patients) were carried out with non-parametric Mann–Whitney test without matching due to the small number of patients in both groups. Comparisons of FcRn expression between the two groups of patients (increased FcRn expression vs. non-increased FcRn expression patients) were carried out with a repeated-measure ANOVA. Multiple comparison tests [Tukey's HSD (honestly significant difference) test] were performed to evaluate the differences in FcRn expression between the two groups during the follow-up of the study. Correlations between FcRn expression and biological data were made with a Spearman's test and linear regression. The relationship between slow graft function and FcRn expression was studied with a Fisher's exact test due to the small number of patients. Comparison of serum IgG levels before and 1 month after transplantation in the two groups was performed using a paired *t*-test. Differences in IgG serum level decrease were compared between the two groups with unpaired *t*-test. Comparisons of the percentage of IgG decrease were made using the non-parametric Mann–Whitney test without adjustment due to non-normality of the data in the two groups.

Guidelines

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Regional University Hospital Center of Tours (ASTRE database, agreement number: DR-2012-518).

Informed consent statement: Informed consent was obtained from all subjects included in the study.

Results

Measurement of FcRn expression in healthy donors

Since FcRn is mainly located in the endosomes, the study of its expression in leukocytes by flow cytometry requires an intracellular staining. We have previously used an anti-human FcRn monoclonal antibody on human leukocytes and on monocytes/macrophages from healthy donors by flow cytometry [32]. We have validated its specificity with another anti-FcRn antibody by Western blot analysis [34]. Non-specific labelling was evaluated with an isotype control antibody included in each flow cytometry experiment. We first established the reference values for FcRn expression in 20 healthy donors from the 'Etablissements Français du Sang'. It was assessed in the total leukocyte population according to the gating strategy shown in Fig. 1. Results are presented as the MFI ratio between anti-FcRn and isotype control staining, a ratio between 1.43 and 2.71 are considered as normal.

Monitoring of FcRn expression in kidney transplant patients

FcRn expression was then longitudinally analysed in 25 kidney transplant patient leukocytes. The clinical data of patients are shown in Table 1. FcRn expression was monitored pre- and post-transplantation over a period of 70 days, with an intensive evaluation during the first week (Fig. 2). During the post-transplantation period, leukocyte FcRn expression was evaluated sometimes up to 4 times to assess the immediate consequences of ischaemia-reperfusion, at the time of the onset of the first rejection phenomena and during the period when rejection may occur.

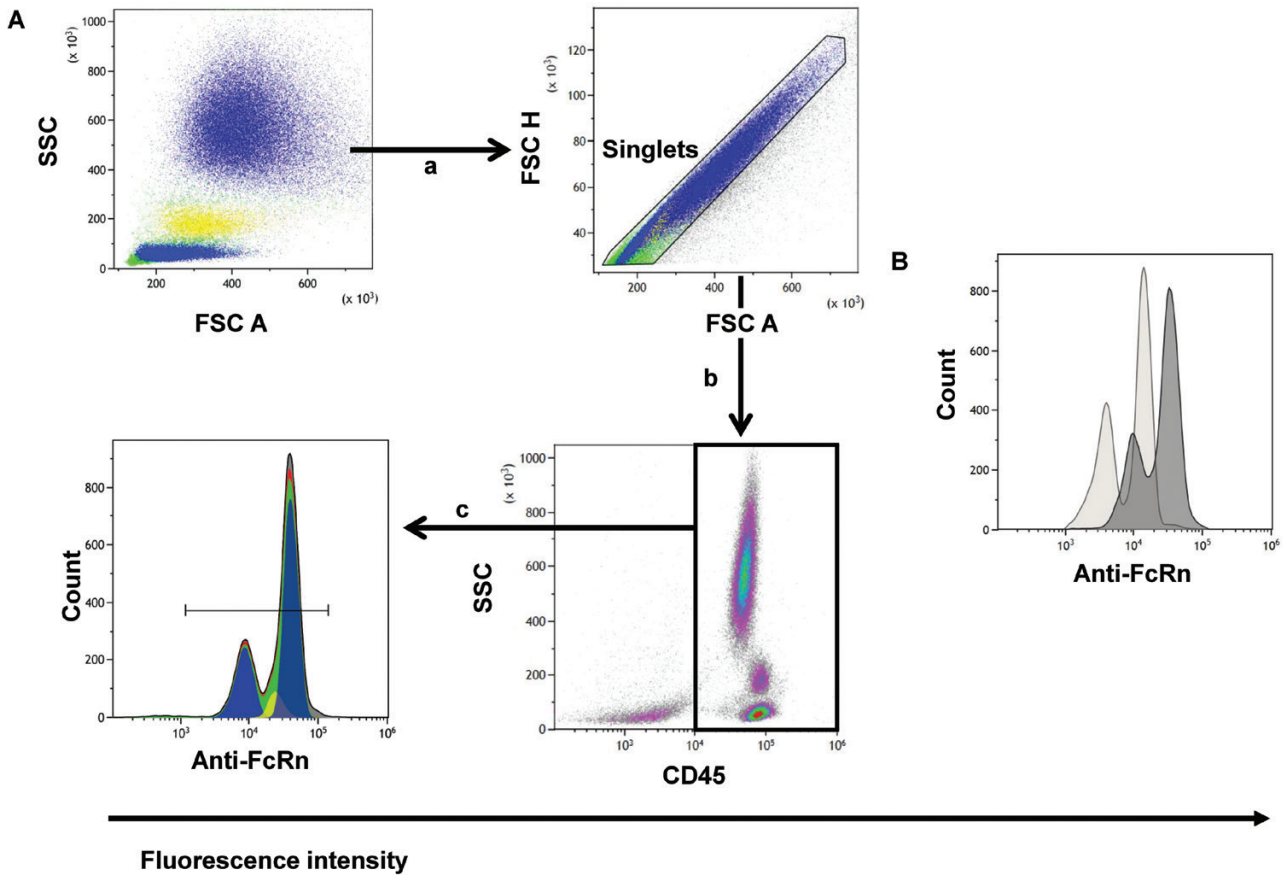

Figure 1. Analysis of FcRn expression in leukocyte populations by flow cytometry. (A) Gating strategy. a: Gating on singlets from FSC/SSC gate. b: Leukocyte gating based on structure (SSC) and CD45 expression. c: Anti-FcRn antibody staining in total leukocyte population. (B) Representative fluorescence intensity of anti-FcRn antibody (dark grey) and isotype control (light grey) for a healthy donor.

Table 1. Clinical data of kidney transplant patients

Patients	$n = 25$
Age (mean ± standard deviation)	53 ± 15
Men	17 (68%)
Women	8 (32%)
Living donors	12 (48%)
Living related donors (brother, sister, children, and father)	6 (24%)
Living unrelated donors	6 (24%)
Non-living donors	13 (52%)
Anti-thymocyte globulin treatment	8 (32%)
Basiliximab induction	17 (68%)
Rank of kidney transplant for each patient	
First transplant	19 (76%)
Second transplant	5 (20%)
Third transplant	1 (4%)

FcRn monitoring allowed us to identify some patients with elevated leukocyte FcRn levels between days 2 and 6 post-transplantation compared to normal levels, leading to the description of two groups of patients (Fig. 2A and B). Nine patients (36%) in the 'increased FcRn expression' group in red had a significantly higher leukocyte FcRn ratio at d2-d6 (Fig. 2A) compared to the 16 patients (64%) in the 'non-increased expression' group in blue ($P < 0.0001$) (Fig. 2B). In the following results, the former group (red) will be referred to as 'increased expression' and the latter (blue) as 'non-increased expression'. This also allowed us to define four different time periods: before transplantation (d-1), between days 0 and 2 post-transplantation (d0–d2), between days 2 and 6 post-transplantation (d2–d6), and after day 6 post-transplantation (>d6). Leukocyte FcRn expression was measured at least once during each period. No difference was noticed between the two groups at d-1, d0–d2, and >d6. Variations in FcRn expression within each group were evaluated during the follow-up of the study. In the 'non-increased expression' group, FcRn expression decreased significantly at d2–d6 compared to d-1 ($P = 0.0035$) and to d0–d2 ($P = 0.0032$). In the 'increased expression' group, FcRn expression increased at d2–d6 compared to >d6 ($P = 0.034$).

Albumin and FcRn expression

To further analyse the parameters associated with the differential leukocyte FcRn expression at d2–d6, we compared albumin concentrations between the two groups, at d-1, d0–d2, d2–d6, and >d6 (Table 2).

While no difference was depicted before kidney transplantation, a significant decrease in albumin concentrations was noticed in the 'non-increased FcRn expression' group compared to the 'increased FcRn expression' group of patients after transplantation ($P = 0.0032$) (Fig. 3A). We then

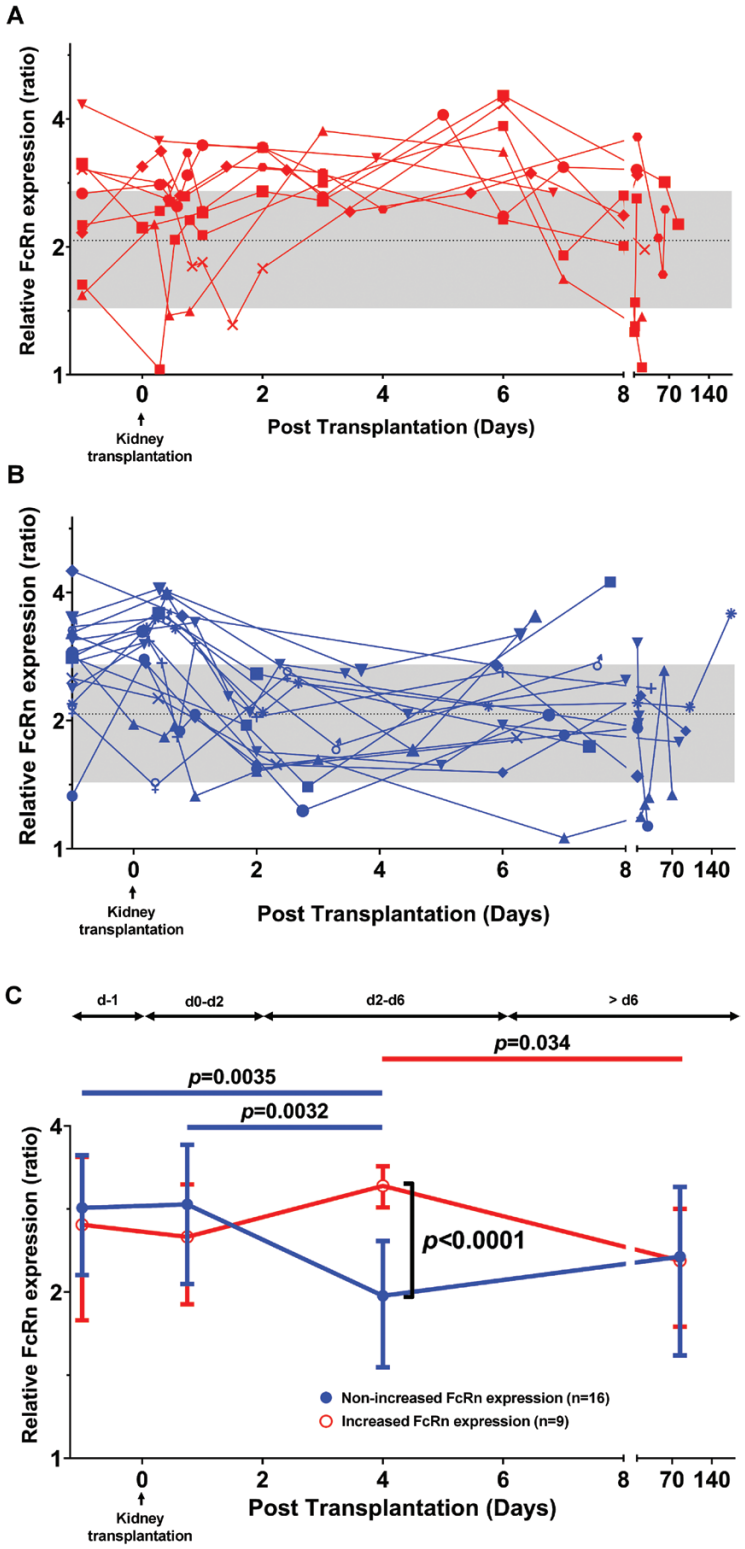

Figure 2. Monitoring of leukocyte FcRn expression in renal transplant patients. Data are expressed as MFI ratio between FcRn staining and isotype control. Each line represents one patient. Horizontal dotted line and grey area represent mean and range of normal FcRn values (1.43–2.71) obtained from 20 healthy donors. FcRn expression in the 'increased FcRn expression' group of patients (in red, $n = 9$, A) and 'non-increased FcRn expression' (in blue, $n = 16$, B) during the follow-up of the study. (C) Monitoring of FcRn expression in the 'non-increased FcRn expression' (blue) or 'increased FcRn expression' (red) group of patients at d-1, d0–d2, d2–d6, >d6. Results are presented as mean ± SD. *P*-values were calculated with repeated measures ANOVA between groups or with Tukey's HSD test within each group.

Table 2. Median albumin concentrations in 'increased FcRn expression' and in 'non-increased FcRn expression' groups during the monitoring of patients

	Increased FcRn expression			Non-increased FcRn expression			*P*[*]
	n	Albumin (g/L)	IQR	n	Albumin (g/L)	IQR	
Before kidney transplantation (d-1)	9	43.0	4.5	16	43.0	2.8	0.85
d0–d2	9	39.0	2.7	16	36.4	5.1	**0.025**
d2–d6	9	35.5	5.1	16	34.1	4.8	0.14
>d6	9	41.0	9.5	16	36.5	7.5	0.13

[*]Significant *P*-value are in bold (Mann–Whitney test).
n: number of values, IQR: interquartile range.

compared albumin concentrations between the two groups during the three post-transplantation periods (d0–d2, d2–d6, and >d6). A significant decrease in albumin concentration was observed in the d0–d2 period between the 'non-increased FcRn expression' and the 'increased FcRn expression' groups of patients ($P = 0.025$) (Fig. 3B), whereas no significant difference was observed at d2–d6 and >d6 periods.

Albumin concentration differences at d0–d2 are likely related to leukocyte FcRn expression differences at d2–d6, as suggested by a correlation ($P = 0.02$) between the two parameters in the whole cohort (Fig. 4) and confirmed by linear regression ($P = 0.0030$).

IgG and FcRn expression

IgG concentrations were not available during the first week after transplantation but were analysed 1 month after transplantation in comparison to pre-transplant values. A significant decrease in IgG concentrations (27.9%) was observed in the entire cohort (–2.97 g/L, $P < 0.0001$), found both in the 'non-increased FcRn expression' group (30.6%, $P < 0.0001$) and in the 'increased FcRn expression' group (22.8%, $P = 0.0036$) (Fig. 5). The difference of decrease between the two groups is not significant (–3.4 g/L vs. –2.1 g/L, $P = 0.06$).

Graft function recovery, creatinine rate, eGFR, and FcRn expression

Only one patient had severe delayed graft function requiring dialysis in the first week after transplantation. We analysed the slow recovery of graft function, defined as creatinine above 250 µmol/L on day 5 after transplantation. No differences were observed between the groups ('increased FcRn expression': 2/9 (22%), 'non-increased FcRn expression': 5/16 (31%); $P = 1$).

We then evaluated whether creatinine and eGFR, which are two biological parameters used to appreciate transplant efficiency, were associated with FcRn variations. Creatinine concentrations were analysed from d1 to d7 (Fig. 6A) post-transplant and eGFR at 1, 2, and 3 months post-transplant (Fig. 6B). There was no difference between the two groups in creatinine concentration at 1 week post-transplant or in eGFR at 3 months post-transplant (Fig. 6).

Warm and cold ischaemia time, donor type, immunosuppressive regimen, and FcRn expression

We evaluated warm and cold ischaemia time in 'increased FcRn expression' and 'non-increased FcRn expression' patients. These parameters are known to influence ischaemia-reperfusion injury, which in turn can activate autophagy. Warm and cold ischaemia times were compared between the two groups. A statistical trend in cold ischaemia time ($P = 0.09$) was observed in 'increased FcRn expression' patients compared to 'non-increased FcRn expression' patients, with a shorter time in the former (Fig. 7A). No difference in warm ischaemia time ($P = 0.65$) was observed between the groups after transplantation (Fig. 7B).

We also assessed FcRn expression in living and non-living donors at each of the previously described time points (d-1, d0–d2, d2–d6, and >d6). FcRn expression was compared between the two groups (Fig. 7C). No difference in FcRn expression was observed at any time after transplantation. Similarly, the immunosuppressive regimens given to the patients had no effect on FcRn expression during the post-transplant period (Fig. 7D).

Discussion

Although kidney transplantation represents a complex situation combining ischaemia-reperfusion injury, graft immune recognition and renal dysfunction, it is an excellent scenario to unmask a possible FcRn dysregulation. We are currently identifying a subgroup of patients with increased FcRn expression between d2 and d6 post-transplant. Albumin first attracted our attention as it is one of the two FcRn ligands, along with IgG. We observed a significant positive correlation between leukocyte FcRn expression at d2–d6 and albumin concentrations at d0–d2 with a statistical trend at d2–d6 and >d6. A transient decrease in albumin concentration has been observed in the first weeks after transplantation [39] and has been associated with acute inflammation [40]. Although TNF-α upregulates FcRn [9, 10], IFN-γ is known to downregulate it [9, 10]. A common inflammatory pathway could contribute to lowering both FcRn expression and consequently albumin concentrations. However, the reverse kinetics (albumin decreases on d0–d2 before FcRn increases on d2–d6) do not support such a common origin. Furthermore, no correlation was found between FcRn expression and C-reactive protein concentrations (data not shown), making this hypothesis rather unlikely. As albumin is a ligand of FcRn, we can hypothesize that a regulatory loop of FcRn levels could be exerted by its ligand, i.e. the higher albumin rates at d0–d2 would increase FcRn levels during the following period d2–d6. This would suggest that in response to variations in albumin concentration induced by kidney transplantation, albumin could regulate FcRn levels, which in turn could help albumin reabsorption in

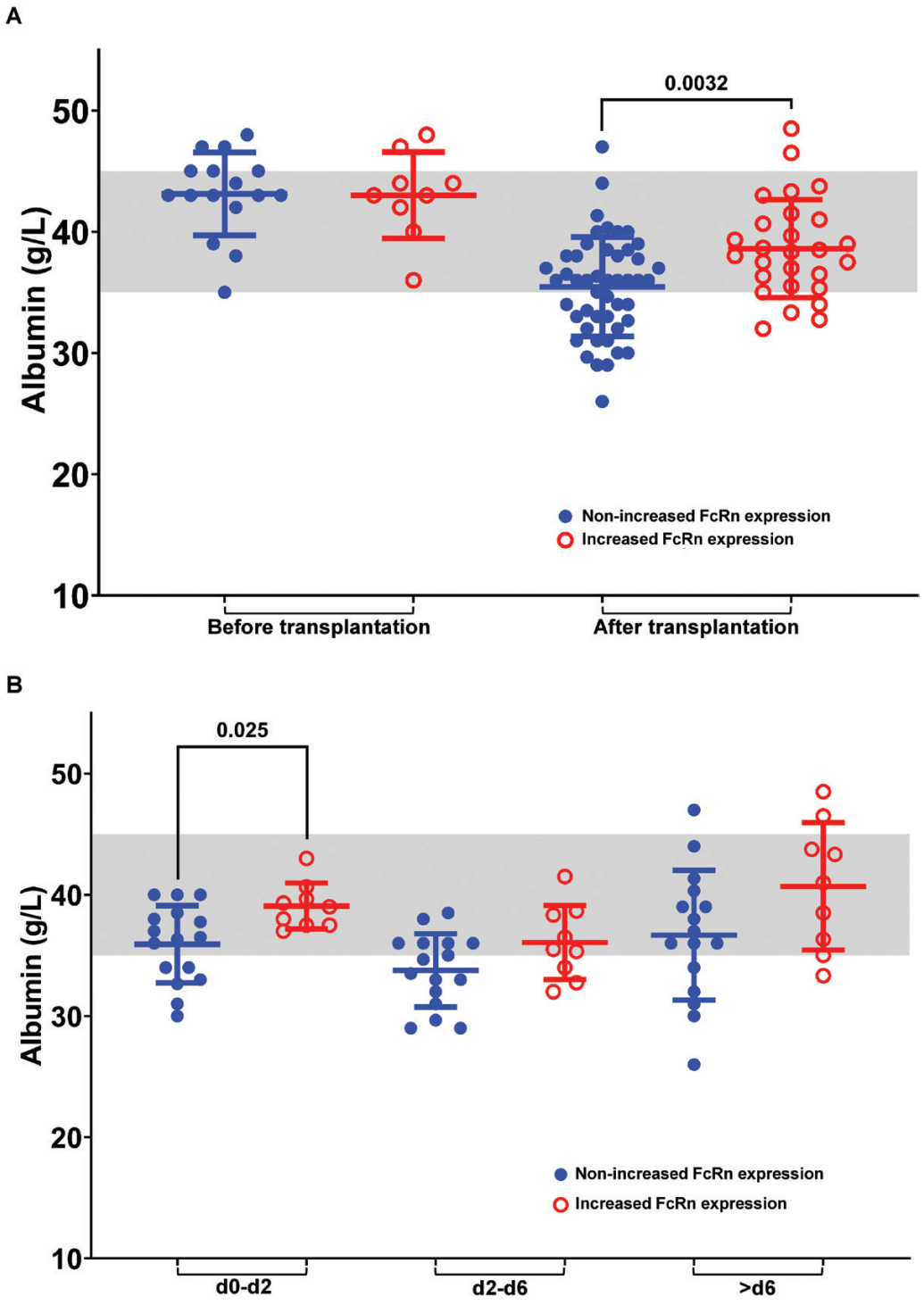

Figure 3. Albumin concentrations in the 'increased FcRn expression' (red) and the 'non-increased FcRn expression' (blue) groups of patients. (A) Before or after kidney transplantation and (B) detailed at d0–d2, d2–d6, >d6 in the serum of 25 patients (mean ± SD). The horizontal grey zone represents the range of normal albumin values [35–45 g/L]. *P*-values (0.0032 and 0.025) were calculated with a Mann–Whitney test.

the proximal tubules. This loop could be either direct or indirect *via* other molecules such as cytokines or albumin-bound proteins that could influence FcRn levels. Further *in vitro* experiments will be performed in order to validate our hypothesis. However, it must be assumed that the variations measured in blood cells are also observed in podocytes or renal tubules.

The role of FcRn in albumin and IgG handling has been studied at the renal level in mice with podocytes knock-out for FcRn [41]. An increase in IgG intraglomerular accumulation was observed, but no change in albumin accumulation was detected, suggesting that the FcRn-mediated trafficking of these proteins is different [41]. This result may be explained by the fact that albumin binds to other molecules such as the

cubilin–megalin complex in clathrin-coated vesicles during the endocytosis phase thus being rescued from degradation [42, 43]. Interestingly, megalin has recently been described to orchestrate FcRn endocytosis and intracellular trafficking [44]. After transplantation, IgG concentrations decrease during the first 2 weeks and then remain slightly decreased [39]. In agreement, we found that IgG concentrations were significantly lower 1 month after transplantation compared to the period before transplantation. A marked decrease in IgG levels was observed in both groups but appeared more important in patients who did not display an increased expression of FcRn. Although the difference in IgG reduction between the two groups was not significant, it suggests that high FcRn expression in leukocytes may well reflect FcRn expression in the endothelium and recycling of IgG. Further studies should provide information on IgG variations during the first days after transplantation according to the expression of FcRn.

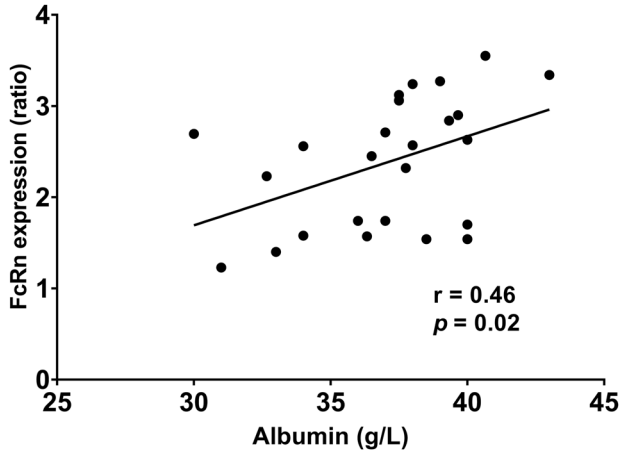

Figure 4. Correlation between FcRn expression at d2–d6 and albumin concentrations at d0–d2 in the whole cohort (n = 25).

Creatinine and eGFR are two markers for estimating renal function, the former in the first days after transplantation (acute variations) and the latter more than 1 month after transplantation. In this study, we followed the evolution of these parameters in relation to FcRn levels in the two groups of patients. No difference in creatinine levels (d1–d7) or in eGFR was observed between the two groups. We also evaluated the effect of immunosuppressive therapy, the induction therapy (basiliximab or thymoglobulin), the origin of the transplant (living donor or non-living donor) and sex or age of the recipients. There were no differences between the groups of patients. We evaluated delayed graft function and slow graft function in our cohort. There was no association between these two parameters and FcRn expression. However, the influence of these parameters cannot be completely excluded due to the small number of patients.

Recently, Uchida *et al.* [33] showed that FcRn colocalizes with ATG7 (autophagy-related 7), an autophagosome protein, in renal tubular epithelial cells. They showed that suppression of autophagy in the tubules impairs FcRn transport, thereby inhibiting albumin transcytosis. Autophagy has also been shown to be induced by hypoxia in proximal tubular cell culture or during renal ischaemia/reperfusion injury [36]. It also attenuates inflammation by downregulating NRLP3 (nucleotide-binding and oligomerisation domain-like receptors) cytokine production [45]. These constitutive or induced mechanisms play a key role in maintaining podocyte integrity [46]. Interestingly, our group has shown that FcRn expression is regulated by autophagy during macrophage differentiation [34]. Therefore, we compared cold and warm ischaemia time, which could activate autophagy and modify FcRn expression according to our recent findings. A statistical trend of lower cold ischaemia time was observed in 'increased FcRn expression' patients compared to 'non-increased FcRn expression' patients, suggesting that this parameter could modify FcRn expression. However, a larger number

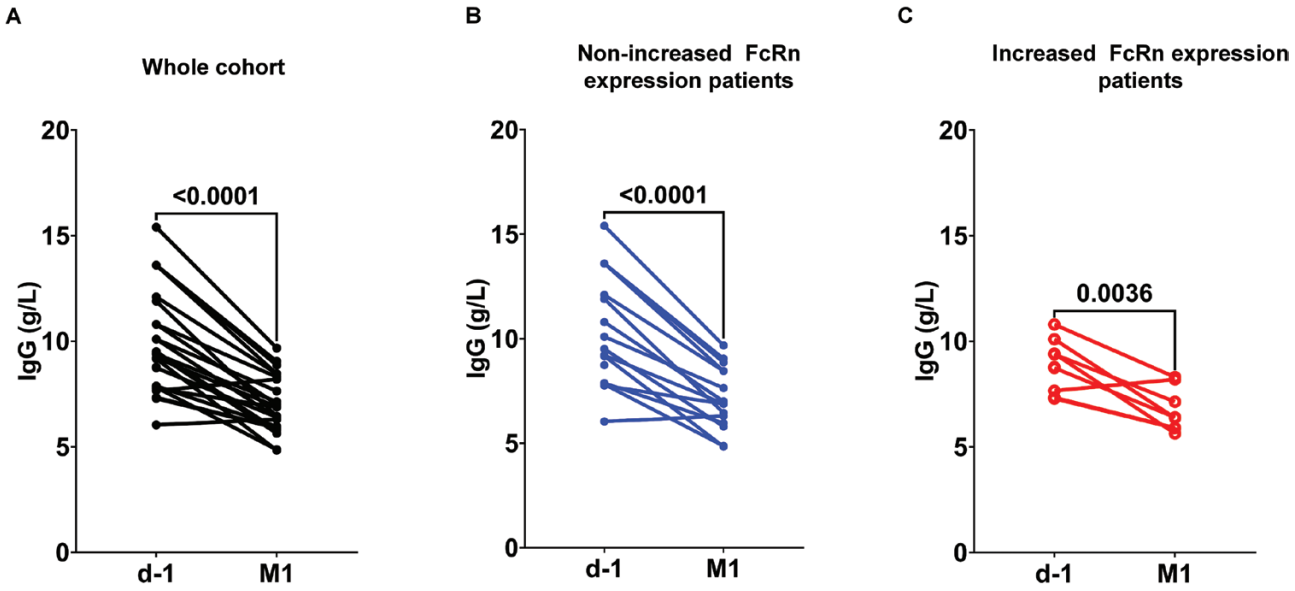

Figure 5. IgG serum levels at d-1 (pre-transplant) and M1 (1 month post-transplant) (A) in the whole cohort, (B) in the 'non-increased FcRn expression' (blue), and (C) in the 'increased FcRn expression' (red) groups of patients. *P*-values (<0.0001 and 0.0036) were calculated with paired *t*-test.

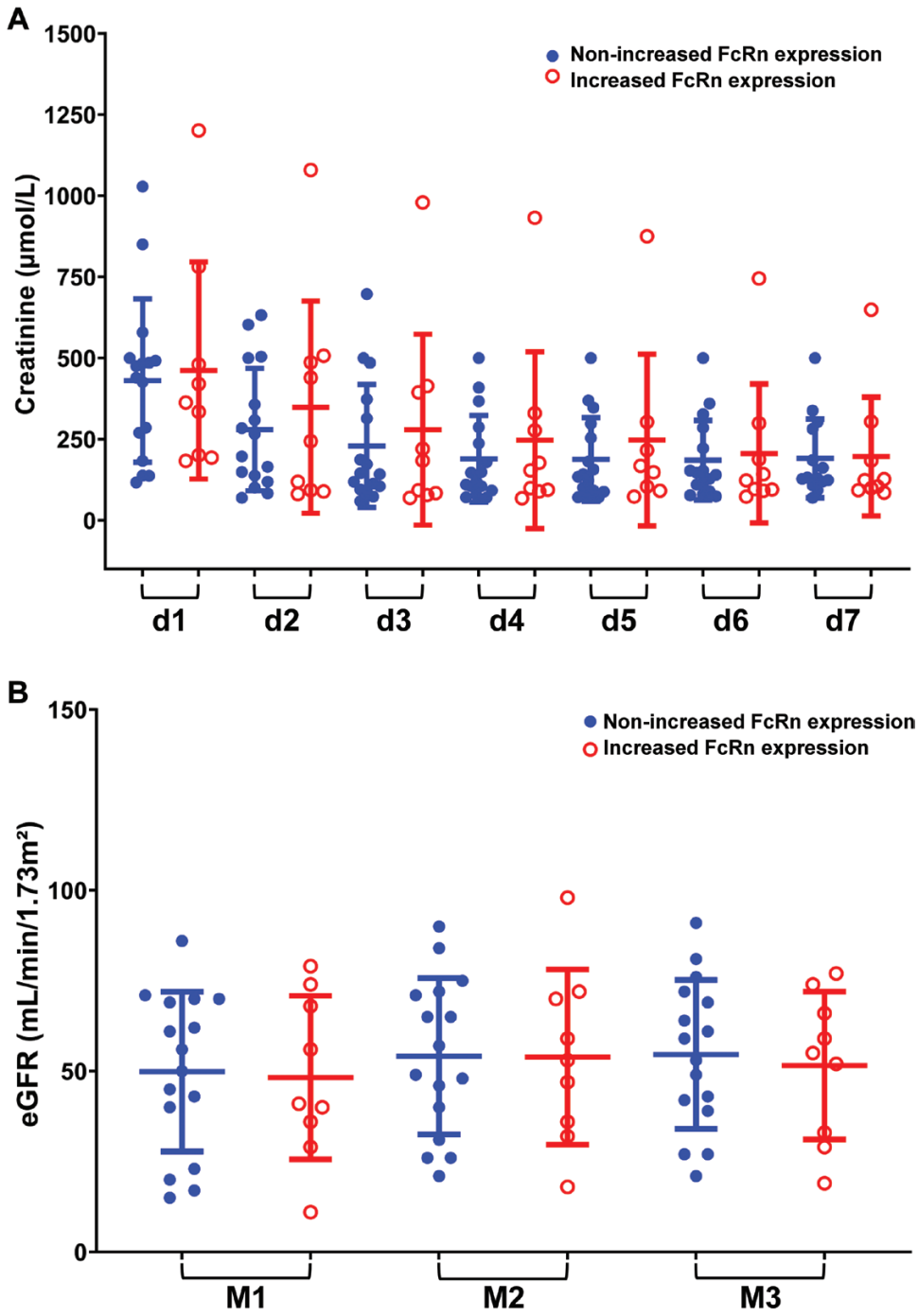

Figure 6. Analysis of serum creatinine and eGFR rate in 'increased FcRn expression' (red) and 'non-increased FcRn expression' (blue) groups of patients after kidney transplantation. (A) Serum creatinine concentrations on day 1 (d1), d2, d3, d4, d5, d6, and d7. We assigned a serum creatinine value of 500 µmol/L to the dialysis patient during the first week. (B) Estimated glomerular filtration rate at 1 month (M1), 2 months (M2), and 3 months (M3) after kidney transplantation. Results are presented as mean ± SD.

of patients need to be included to confirm this hypothesis. Taken together, these data suggest a link between FcRn expression, ischaemia/reperfusion, and autophagy. We could hypothesize that ischaemia/reperfusion during transplantation induces autophagy, which could modulate FcRn expression and albuminemia.

In conclusion, we found that albumin concentrations measured early after transplantation at d0–d2 influence FcRn expression at d2–d6, raising new questions about the mechanisms underlying these original observations.

Acknowledgements

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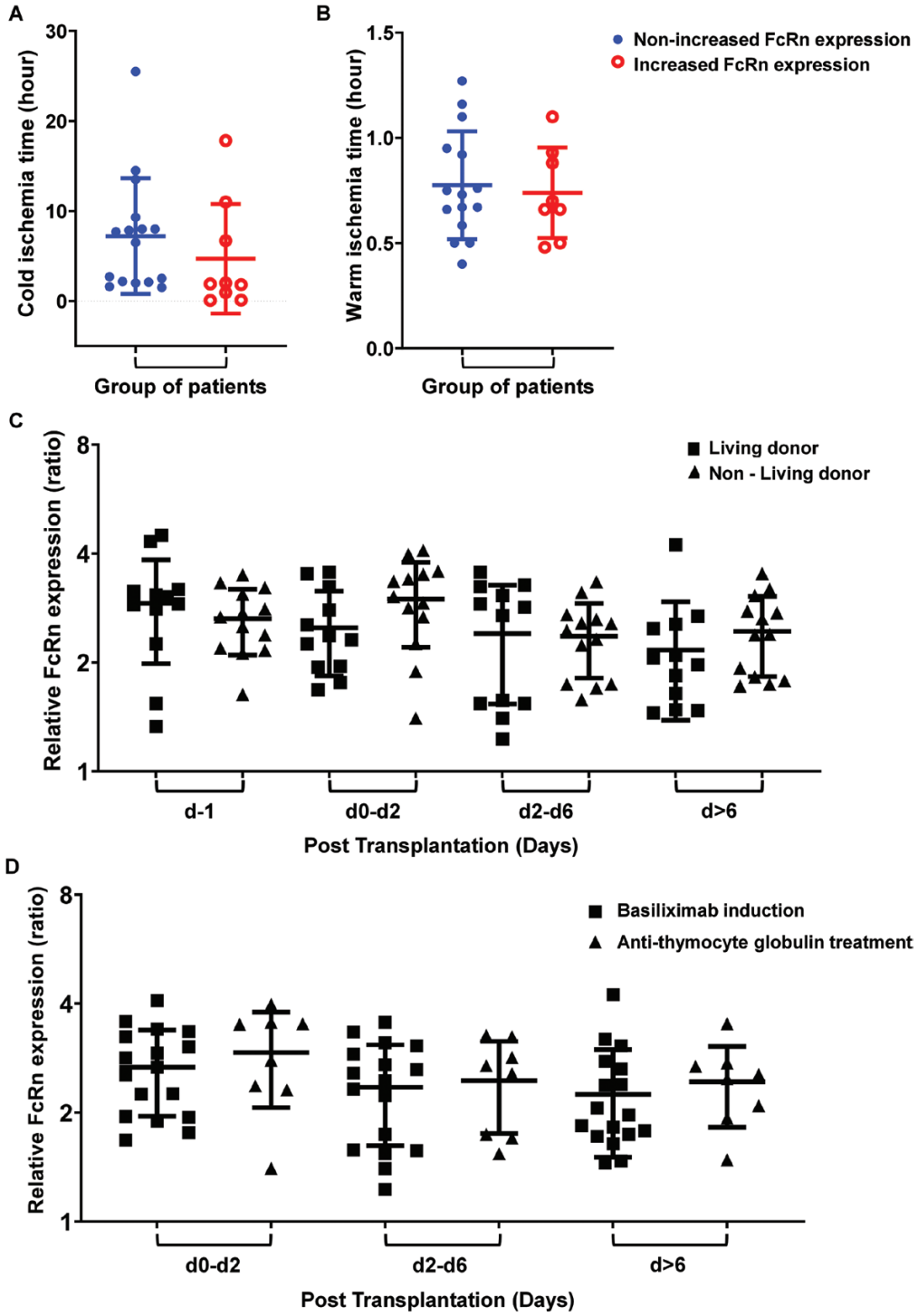

Figure 7. Analysis of ischaemia time in 'increased FcRn expression' (red) and 'non-increased FcRn expression' (blue) groups of patients after kidney transplantation. (A) Cold ischaemia time. (B) Warm ischaemia time. (C) FcRn expression in living and non-living donors after kidney transplantation at d-1, d0–d2, d2–d6, and >d6. (D) FcRn expression in the post-transplant period according to immunosuppressive regimens (basiliximab or anti-thymocyte globulin treatment). Results are presented as mean ± SD.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Regional University Hospital Center of Tours (ASTRE database, agreement number: DR-2012-518). Informed consent statement: Informed consent was obtained from all subjects included in the study.

Conflict of interests

None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Investigation: P.B., J.L., B.P., M.-V.D., R.L., J.C.; methodology: P.B., P.G. and V.G.-G.; visualization: P.B.; formal analysis: P.B., N.A., and V.G.-G.; original draft preparation and funding acquisition: V.G.-G. and P.B.; review and editing: V.G.-G., H.W., and P.G.; conceptualization, supervision, and validation: V.G.-G. All authors have read and agreed to the published version of the manuscript.

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