Transplant International

ORIGINAL ARTICLE

The association between killer-cell immunoglobulin-like receptor (KIR) and KIR ligand genotypes and the likelihood of BK virus replication after kidney transplantation

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SUMMARY

BK virus is a common opportunistic post-transplantation viral infection. Although some risk factors have been studied in this context, the contribution of NK cells has not been assessed in detail. In a group of kidney transplant recipients, we studied the association between (i) the likelihood of BK virus replication during the two-year period after kidney transplantation and (ii) the genotypes of the killer cell immunoglobulin-like receptor (KIR) repertoire and their human leukocyte antigen (HLA) ligands. Other clinical factors (such as defective organ recovery and immunosuppressive treatment) were also assessed. BK virus replication was observed in 43 of the 103 recipients (41%). Patients with BK virus replication in the plasma were more likely to display defective organ recovery in the first seven days post-transplantation. BK virus replication was not associated with Missing KIR ligands. However, BK virus replication was more frequent in patients with responsive NK cells (i.e. when a ligand for activating KIRs was not homozygous in the recipient and present in the donor). Our results suggest that defective organ recovery and the recipient's activating KIR repertoire may be related (depending on HLA ligands present in the couple recipient / donor) to the reactivation of BK virus replication after kidney transplantation.

Transplant International 2016; 29: 1168–1175

Key words
BK virus, human leukocyte antigen, kidney transplantation, killer-cell immunoglobulin-like receptor, natural killer cell

Received: 28 January 2016; Revision requested: 25 February 2016; Accepted: 27 July 2016;
Published online: 12 September 2016

Introduction

BK virus is a common opportunistic post-transplantation viral infection and is known to cause interstitial nephritis and allograft failure in renal transplant recipients [1]. Primary infection is acquired in childhood, and BK virus is near-ubiquitous in adults (with a seroprevalence of >80%). After primary infection, the virus becomes latent in the uroepithelium and renal tubular epithelial cells. In immunosuppressed patients, BK virus reactivates mostly within 12 months of transplantation and can induce BK-virus-associated nephropathy (BKVAN) with tubular cell lysis and viruria. Approximately one-third of patients with viruria

doi:10.1111/tri.12820

will develop BK viremia, which (if the dose of immunosuppressant is not reduced accordingly) may progress to nephropathy. In view of the current lack of effective antiviral therapies for BK virus, a better understanding of the risk factors leading to intensive BK virus replication is required.

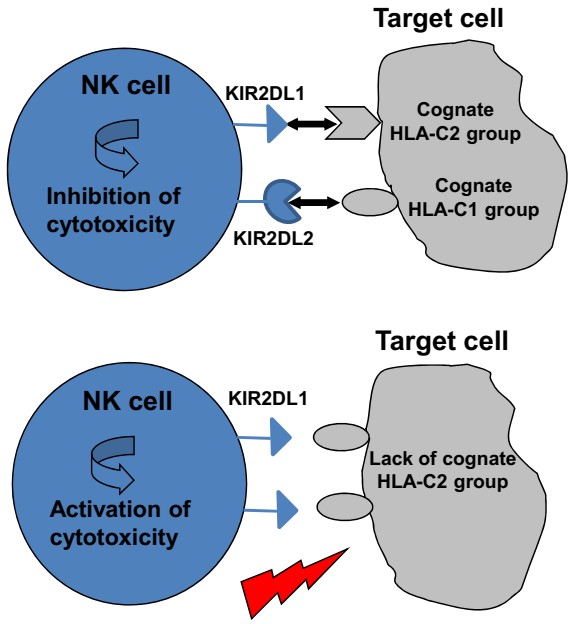
Natural killer (NK) cells contribute to effective innate immune responses and constitute an important line of defense against viruses. NK cell activity and functions are controlled by a complex repertoire of cell surface molecules, including the killer-cell immunoglobulin-like receptors (KIRs). KIR genes encode cell surface glycoproteins present on NK cells and subpopulations of thymus-derived (T) lymphocytes. Unlike T-cell receptor, KIRs are not able to recognize specific antigens but can recognize human leukocyte antigen (HLA) class I subtypes. KIR molecules may possess two (KIR2D) or three (KIR3D) immunoglobulin-like extracellular domains. Inhibitory KIRs (iKIRs) have a long intracellular region possessing inhibitory motifs (KIR2DL, KIR3DL), whereas activating KIRs (aKIRs) have short intracellular tail (KIR2DS, KIR3DS). iKIRs include KIR2DL2/3, KIR2DL2, and KIR3DL1, which respectively recognize peptides from HLA-C alleles with asparagine 80 (the HLA-C1 group; e.g., HLA-C*01, *03, *07 and *08), HLA-C alleles with lysine 80 (the HLA-C2 group; e.g., HLA-C*02, *04, *05, and *06) and HLA-B alleles containing a Bw4 epitope (Fig. 1). aKIRs include KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, and KIR3DS1, which can also bind to HLA class I alleles but do so with lower affinity than the inhibitory KIRs [2]. Furthermore, KIR genes are organized into KIR A and B haplotypes. Group B haplotypes contain additional activating KIR genes and are characterized by the presence of one or more of the following genes: KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DS1. Conversely, group A haplotypes lack all of these genes. Along with the "framework loci" common to both haplotypes, the KIR haplotype A carries only one activating KIR (KIR2DS4) (http://www.ebi.ac.uk/ena).

NK cells preferentially kill cells with low or no human leukocyte antigen (HLA) class I expression; this prompted the "missing-self" hypothesis for iKIRs in humans. The NK cells are de-inhibited when they interact with cells with inappropriate HLA expression (Fig. 1). Indeed, iKIRs detect changes in HLA class I expression induced on the surface of cells by viral infection or malignant transformation. In fact, they bind HLA class I molecules on normal cells and thus protect against lysis by NK cells. The recognition of self-HLA-I molecules by inhibitory KIRs is involved in calibration of the NK cells' effector capacities during differentiation and maturation (i.e., licensing) [3]. Infected or transformed cells often lose their HLA class I expression fully or partly, which thus exposes them to NK cell attack. Moreover, in kidney transplantation, the transplant and recipient are often HLA class I-mismatched. This enables donor target cells lacking HLA-I to be recognized as "missing-self" by the recipient's licensed NK cells. This situation is made even more complex by the fact that NK cells are stimulated by a number of different activating receptors, such as aKIRs and receptors for a variety of ligands on potential target cells. However, it is hard to see how NK cells could express activating receptors that bind to ligands expressed on healthy cells, since this interaction might lead to autoreactivity. One hypothesis holds that NK cells expressing activating KIRs are rendered hyporesponsive if the ligand is present in the host. Indeed, in HLA-C2 homozygous individuals, NK cells expressing KIR2DS1 in the absence of self-HLA class I-specific KIRs were found to be hyporesponsive to target cell stimulation (whereas no such hyporesponsiveness was observed in HLA-C1 homozygous individuals) [4]. Over the last decade, a number of studies have sought to establish whether KIRs have a role in combating viral infections. It has been previously reported that aKIRs have protective effects against BK-virus-associated nephropathy in renal transplant patients [5] and that lack of HLA-Cw7 in the donor and the recipient was associated with a susceptibility to develop BK virus [6]. In the present study, we hypothesized that a missing-self context and/or a KIR group B haplotype were associated with a significant impact in the incidence of BK virus replication. Therefore, we studied the association between recipient KIR and donor HLA genotypes with regard to the iKIR "missing-self" hypothesis, the number of aKIRs and more "responsive" situations, the clinical risk factors, and the risk of BK virus replication (which is not necessarily associated with histologically confirmed graft nephropathy) in a cohort of 103 kidney transplant recipients.

Materials and methods

Patients

This retrospective study was approved by the local independent review boards. Before transplantation, all recipients gave their informed consent to participation in potential studies using molecular samples and biological and clinical data. We included patients who



KIR	KIR Ligand Group	KIR Ligand HLA alleles
KIR2DL1 KIR2DS1	**Group 2 HLA-C alleles** (Lysine residue at position 80 in α1 helix of HLA-C molecule)	C*02, C*04, C*05, C*06, C*07:07, C*07:09, C*12:05, C*15 (except C*15:07), C*16:02, C*17, C*18
KIR2DL2 KIR2DL3	**Group 1 HLA-C alleles** (Asparagine residue at position 80 in α1 helix of HLA-C molecule)	C*01, C*08, C*13, C*15 :07, C*03 (except C*03 :07, C*03:10, C*03:15), C*07, C*12 (except C*12:05), C*14, C*16 (except C*16 :02)
KIR3DL1 (KIR3DS1?)	**Group HLA-Bw4 alleles**	A*23, A*24, A*25, A*32, B*13, B*17, B*27, B*37, B*38, B*44, B*47, B*49, B51, B*52, B*53, B*58, B*59, B*63, B*77, B*15
KIR3DL2	**Group HLA-A alleles**	A*03 A*11
KIR2DL4	**Group HLA-G alleles**	
No ligands have been detected to date for the remaining KIR molecules (KIR2DL5, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DL3)		
Source: the IMGT-HLA database at http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/		

Figure 1 The concept of NK cell activity and the "missing-self" hypothesis. Some of the inhibitory KIRs (such as KIR2DL1/2DL2/2DL3 and KIR3DL1/3DL2) recognize specific HLA major histocompatibility complex class I molecules (including HLA-A, HLA-B, HLA-C, and HLA-G) and thus inhibit cytotoxicity. Failure to recognize the appropriate KIR ligand on a mismatched cell triggers NK-cell-mediated cytotoxicity.

underwent kidney transplantation consecutively between 2010 and 2013, with at least 24 dialysis-free months of clinical and virologic follow-up after transplantation (i.e., no allograft loss). Our center did not record graft loss due to BKVAN during this period. A total of 103 kidney transplants patients were included. All patients were equipped with a double J ureteral catheter for the first month after transplantation. All patients underwent a kidney biopsy 4 months after transplantation and were screened for BK viruria at least twice during the first 12 months after transplantation and/or if kidney function deteriorated. Upon detection of the virus in urine, plasma samples were also screened for the presence and load of BK virus. A patient was considered to be positive for BK virus replication in urine (U) or plasma (P) sample if the virus was detected in two consecutive samples collected 1 month apart. Patients in whom BK virus was never detected constituted the U^-P^- group. If BK virus DNA was detected in the urine sample only, the patient was classified into the U^+P^- group. Lastly, if BK virus DNA was detected in both urine and plasma, the patient was classified into the U^+P^+ group. We also recorded age, gender, and other clinical data (such as immunosuppressive therapy performed during induction or during humoral graft failure, cold ischemia time, and defective organ recovery and dialysis performed during the first 7 days and/or a creatinine level above 275 μmol/l on day 5).

Nucleic acid extraction and real-time PCR

Viral DNA was extracted from 200 μl samples of urine (U) or plasma (P) by using a specific protocol with the NucliSENS easyMAG system (BioMérieux, Paris, France). BK virus DNA was amplified on an ABI Prism 7500 SDS system (Life Technologies, Saint-Aubin, France), using the BK Virus R-gene® Real-time PCR kit. We used the following viral load thresholds: >5 log10 copies/ml for viruria and >3 log10 copies/ml for viremia.

HLA and KIR genotyping

DNA was obtained from recipient peripheral blood leukocytes and donor splenic lymphocytes by GenoM6 extraction (Qiagen AG, Basel). For donors and recipients, we genotyped HLA-A, HLA-B, HLA-DRB1 and HLA-DQB1 using sequence-specific primed PCR-SSP (Bionobis, Guyancourt, France) and HLA-C by sequence-specific oligonucleotide primed PCR (One Lambda, Canoga Park, CA). For the recipient's KIR repertoire, the analysis was performed using sequence-specific oligonucleotide PCR (One Lambda) for the inhibitory receptors KIR2DL1, 2DL2, 2DL3, 2DL5, and 3DL1, and the activating receptors 2DL4, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, and 3DS1. Framework genes (KIR3DL3, KIR2DLA4, KIR3DP1, and KIR3DL2) found in all haplotypes were not included in the present

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analysis. Patients with missing KIR ligands were also defined, as HLA-C1, HLA-C2, and/or Bw4 ligands missing in the donor but present (along with the corresponding inhibitory KIR) in the recipient.

Statistical analysis

Statistical analysis was performed using R and GraphPad Prism software, La Jolla, CA, USA. The BK virus load was expressed in $\log_{10}$ copies per milliliter. Continuous variables are expressed as the median [interquartile range (IQR)]. A Kruskal–Wallis test was used for intergroup comparisons of mean values of continuous variables; if a significant difference was observed, a Wilcoxon test was then applied. A chi-squared test was applied for categorical variables. A Jonckheere trend test was performed in order to compare three groups of patients (classified according to the "intensity" of viral reactivation).

Results

Defective organ recovery is associated with a greater likelihood of BK plasma replication after kidney transplantation

The demographic characteristics of the 103 study participants are summarized in Table 1. Qualitative PCR analysis of BK virus in U and P detected 43 (41%) positive urine samples during the first 24 months after kidney transplantation and 22 (21%) positive plasma samples. It is noteworthy that all recipients with a positive plasma sample had a positive urine sample. Given that renal biopsies were performed very soon (4 months) after transplantation, no cases of BK-virus-associated nephropathy were observed. According to the practices of our center, no biopsy was available thereafter.

The proportion of defective organ recovery in the first 7 days post-transplantation appeared to be related (at least in part) to the above findings because it was higher in U^+P^+ patients than in U^-P^- or U^+P^- patients ($P = 0.02$). The three BK virus patient groups did not differ significantly in terms of the type of immunosuppressive therapy administered during induction. Only four patients were treated for humoral acute rejection prior to BK viruria and/or viremia, and three of these remained negative for BK virus thereafter.

There were no significant differences between the U^+P^+ and U^+P^- groups in terms of most of the other clinical variables (donor age, donor gender ratio, recipient nephrectomy, and a history of transplantation). However, the proportion of patients with a urine viral load above 8 $\log_{10}$ was higher in the U^+P^+ group (95%) than in the U^+P^- group (38%; $P < 0.001$). Viremia lasted for more than 6 months in 15 of the 22 positive patients (68%).

Activating KIRs may be associated with a significant higher rate of BK replication in a more "responsive" context

We did not observe a significant impact of KIR haplotype A versus B on the incidence of BK virus replication. Moreover, the incidence of BK virus replication did not depend on the number of activating KIR genes (among KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, and KIR3DS1). By using a Jonckheere trend analysis to compare our three patient groups (classified according to the "intensity" of the viral reactivation), we observed a significant higher rate of BK replication (U^+ versus U^-, $P = 0.04$) in two "responsive" situations ($KIR2DS1^+$ and nonhomozygous HLA-C2 in the recipient and $HLA\text{-}C2^+$ in the donor, and $KIR2DS2^+$ and nonhomozygous HLA-C1 and donor $HLA\text{-}C1^+$). There was no significant difference for $KIR3DS1^+$ HLA-Bw4/$Bw6^+$ or Bw6/$Bw6^+$ recipients with $HLA\text{-}Bw4^+$ donors.

Missing KIR ligands are not associated with a lower incidence of BK virus replication in the months following kidney transplantation

Recipient KIR and donor HLA genotypes were defined and assessed in relation to BK virus replication in urinary or plasma samples (Table 2). There were no significant differences with regard to HLA-A, HLA-B, HLA-DRB1, or HLA-DQB1 mismatches or donor C*07 status. The donor's missing KIR ligands were then determined accordingly: Recipient NK cells that express an inhibitory KIR specific for self-HLA class I are functionally competent and target donor cells that lack this self-HLA class I molecules. We considered the following three situations: a $KIR2DL1^+$/$HLA\text{-}C2^+$ recipient and an $HLA\text{-}C2^-$ donor; a $KIR2DL2/2DL3^+$/$HLA\text{-}C1^+$ recipient and an $HLA\text{-}C1^-$ donor; and $KIR3DL1^+$/$HLA\text{-}Bw4^+$ recipient and an $HLA\text{-}Bw4^-$ donor. Missing KIR ligands were analyzed with regard to the incidence of BK virus replication in the urine and the plasma during the first 24 months after transplantation (i.e., U^-/P^- versus U^+/P^- and/or U^+/P^+). We did not find a significant relationship between the presence of one or two missing KIR ligands and the incidence of BK virus replication – even when data for P^- and P^+ cases were pooled.

Table 1. Clinical and virologic characteristics of the study participants and subgroups.

Patients	Total	U^-P^-	U^+P^-	U^+P^+
Number	103	60	21	22
Donor age (years), median (IQR)	52 (20.5)	52 (17)	47 (28)	48 (22.75)
Donor gender (male/female)	53/45	35/22	8/13	10/10
Recipient age (years), median (IQR)	51 (21.75)	52 (17.5)	48 (21)	47 (22.75)
Recipient gender (male/female)	62/41	35/25	13/8	14/8
HLA-A, HLA-B, HLA- HLA-DRB1, HLA-DQB1 mismatches, median (IQR)	5 (3)	5 (2)	4 (3)	5 (3)
Cold ischemia time in minutes, median (IQR)	825 ± 309	818 ± 297	736 ± 340*	920 ± 372*
Nephrectomy	17 (16.5%)	10 (16.6%)	3 (14.3%)	4 (18.2%)
Previous transplantation	17 (16.5%)	9 (15%)	3 (14.3%)	5 (22.7%)
Calcineurin inhibitors				
Tacrolimus	91 (88.3%)	53 (88.3%)	17 (81%)	21 (95.5%)
Cyclosporine	12 (11.7%)	7 (11.7%)	4 (19%)	1 (4.5%)
Induction therapy				
Antithymocyte globulin	38 (36.9%)	24 (40%)	6 (28.6%)	8 (36.4%)
Basiliximab	65 (63.1%)	36 (60%)	15 (71.4%)	14 (63.7%)
Urine BK virus load > 8 (log_{10} copies/ml)	29 (28.2%)	NA	8 (38.1%)	21 (95.5%)**
Patients with a serum creatinine level >275 μmol/l at D5 post-transplant	40 (38.8%)	18 (30%)	8 (38%)	14 (63.6%)***

R, recipient; D, donor; U, urine; P, plasma; NA, not applicable; IQR, interquartile range.

*$P = 0.04$ for U^+P^- versus U^+P^+.

**$P < 0.001$ for U^+P^- versus U^+P^+.

***$P = 0.02$.

Table 2. KIR and KIR ligand genotypes and BK virus detection in the study population.

Patients	Total	U^-P^-	U^+P^-	U^+P^+
Number	103	60	21	22
Donor HLA-C*07 negative	65 (63%)	41 (68%)	12 (57%)	12 (54%)
KIR haplotype AA	28 (27%)	18 (30%)	5 (24%)	5 (23%)
KIR haplotypes AB+BB	75 (73%)	42 (70%)	16 (76%)	17 (77%)
Number of recipient KIR activators				
≤3	62 (60%)	37 (62%)	11 (52%)	14 (64%)
>3	41 (40%)	23 (38%)	10 (48%)	8 (36%)
R: $KIR2DS1^+C1^+$ D: $C2^+$	20 (19.5%)	7 (12%)	7 (33%)	6*** (27%)
R: $KIR2DS2^+C2^+$ D: $C1^+$	33 (32%)	14 (23%)	12 (57%)	7*** (32%)
R:$KIR3DS1^+Bw6^+$ D: $Bw4^+$	22 (100%)	10 (45%)	5 (23%)	7 (32%)
Missing (C1/C2/Bw4)				
0	62 (60%)	36 (60%)	13 (62%)	13 (59%)
1	34 (33%)	20 (33%)	5 (24%)	9 (41%)
2	7 (7%)	4 (7%)	3 (14%)	0

The KIR haplotypes are defined in the Results section of the main text. KIR ligands were defined by the HLA-C and HLA-Bw status.

***$P = 0.04$ for U^- versus U^+ (U^+ includes both U^+/P^- and U^+P^+).

Outcomes for BK-virus-positive patients

A total of 43 patients were positive for BK virus during the first 24 months after transplantation. The average viral load peaks were as follows: 8.9 log in urine and 4.5 log in plasma. Not all had biopsy-confirmed, BK-virus-associated nephropathy. In the overall study population, 29 patients had a high viral load in plasma or in urine or were persistently positive for BK virus (i.e., for more than 6 months) and could been diagnosed with "suspected BKVAN." This condition partially resolved (i.e., with subsequent clearance of BK virus from both plasma and urine) after reducing the level of immunosuppression. At the last examination available, three patients still had persistent viremia and the virus was still present in the urine of 19 patients.

Discussion

Natural killer cells gain their functionality through a licensing process that depends on KIR-mediated recognition of self-HLA class I molecules during differentiation and maturation. This enables cells lacking HLA-I (such as viral infected cells or, in the context of kidney transplantation, donor cells with an HLA mismatch) to be recognized as a "missing-self" target. Recipient NK cells have been found to display increased *ex vivo* cytotoxicity against donor cells 3 days after kidney transplantation, and this increase appeared to depend on the number of activating KIR genes in the recipient (i.e., genes encoding receptors that potentially recognized donor HLAs) [7]. However, an extensive assessment of donor–recipient KIR ligand gene compatibility/incompatibility did not evidence an effect on renal transplant rejection [8]. The importance of NK receptors in antiviral immunity has already been demonstrated in a mouse model of CMV infection, where Ly49H (a rodent ortholog of the human KIR family) was crucial for elimination of the virus by targeting m157 (an MHC-like protein of viral origin) [9]. In humans, distinct KIR/HLA ligand combinations may be associated with differing susceptibility to infection.

In the present study, we investigated the relationship between NK cell genotype and BK virus replication in a cohort of 103 kidney-transplanted recipients. Our analysis of the recipient KIR and donor HLA genotypes in a missing-self context did not suggest that the absence of HLA ligands for KIR inhibitory receptors and a high number of KIR activating receptors were associated with a significant reduction in the incidence of BK virus replication. Similarly, in the particular context of BKVAN, Trydzenskaya *et al.* did not find any associations between certain KIR/HLA matches and disease—although they had not considered KIR/KIR ligands according to the "missing-self" concept [4]. In contrast, analysis of activating receptor genotypes revealed the

presence of a significantly higher percentage of patients bearing low numbers (≤3) of activating KIR genes in the BK-virus-associated nephropathy group. More precisely, they reported that the lack of the activating receptor KIR3DS1 was a risk factor for nephropathy. Moreover, the kidney may already be irreversibly injured by the time a biopsy reveals BK-virus-associated nephropathy.

The most consistently identified risk factor for the development of BK virus nephropathy is the overall degree of immunosuppression [10]. In our study, immunosuppressive therapy type during induction such as treatment for acute rejection has no impact on virologic data. Note that all patients were on prednisone maintenance.

Other putative risk factors for BK virus nephropathy include male gender, older recipient age, rejection episodes, the degree of HLA mismatch, prolonged cold ischemia, BK serum status, and ureteral stent placement [10, 11]. Our study results showed that plasma replication of BK virus was associated with defective organ recovery during the first 7 days post-transplantation. Moreover, BK virus replication in urine and/or plasma is related to a more responsive NK cell context, *that is,* a KIR2DS1$^+$ HLA-C1/C2$^+$ or C1/C1$^+$ recipient and an HLA-C2$^+$ donor, or a KIR2DS2$^+$ HLA-C1/C2$^+$ or C2/C2$^+$ recipient and an HLA-C1$^+$ donor. However, NK cells have an important role in combatting viral infection by cytolysis of virus-infected cells and NK cells also have a key regulatory role in shaping adaptive immune responses. Our present study results are controversial because we observed more BK virus replication in more responsive NK populations. Controversial because the association of KIR and HLA genotypes in kidney transplantation has mainly been studied in the context CMV disease; the missing KIR ligand's protective effect against CMV infection was prominent during the first 3 months post-transplantation but decreased over time. At 12 months, a high number of activating KIRs result in better protection against CMV [12]. In a group of 90 CMV-negative patients having received a first renal transplantation from a CMV-positive donor, there was no significant difference between the KIR A and B haplotypes or the number of activating or inhibitory KIRs in terms of the occurrence of CMV disease [13]. About BK virus, Tonnerre *et al.* found a lower incidence of BK virus reactivation in recipient transplanted with renal graft carrying MICA A5.1 mutant (a ligand for the activating NK receptor NKG2D) [14]. These data suggest that intragraft MICA expression may a significant incidence on BK virus reactivation after transplantation and may indicate a protective role for MICA A5.1.

Our results can be explained by the limitations of our study, including the relatively small subgroup sizes (particularly for patients with persistent reactivation) and the difficulty in exhaustively describing all potential causes of BK virus reactivation. Moreover, our center takes account of molecular biological proof of BK virus positivity when deciding on a reduction in the level of immunosuppression; we do not perform a kidney biopsy in this context. Moreover, NK cells can react against the graft by several mechanisms such as the missing-self concept but also by inflammation. Indeed, following allorecognition, activated NK cells acquire cytolytic effector functions and release a series of proinflammatory cytokines including IFN-γ and TNF-α [15]. NK cells can promote or suppress inflammation by helping to recruit and activate other immune cells. It has been shown that BK virus replicates prolifically under inflammatory and immunosuppressed conditions, causing inflammation along the genitourinary tract and progressing to tubulointerstitial nephritis with lymphoplasmacytic infiltrates.

Hence, these specific activating KIR/HLA class I genotype interactions may be responsible for susceptibility to the emergence of BK replication (accentuated by *in situ* inflammatory conditions, perhaps), but its effect on the issue such as BK viral load clearance, protective role against nephropathy is not elucidated by our study.

In conclusion, our results suggest that defective organ recovery and the recipient's activating KIR repertoire (KIR2DS1$^+$ and nonhomozygous HLA-C2 in the recipient and HLA-C2$^+$ in the donor, and KIR2DS2$^+$ and nonhomozygous HLA-C1 and donor HLA-C1$^+$) may be related to the reactivation of BK virus replication after kidney transplantation. Taken as a whole, these emphasize the complexity of the NK cell's clinical impact on viral infections after kidney transplantation. Moreover, most studies have assessed genetic parameters and therefore failed to provide direct, functional evidence of a role for activating KIRs in protecting against or increasing susceptibility to viral infections.

Authorship

EB and NG: designed and performed experiments, analyzed and interpreted data, performed the statistical analysis, and wrote the paper; JD and IDA: performed experiments; CP, GF, SC, PFW and GC: provided clinical data and reviewed the manuscript for critical content.

Funding

This work was funded by the Amiens University Hospital as part of the French government's program for hospital-based clinical research.

Conflicts of interest

The authors have declared no conflicts of interest.

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