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Protection From Varicella Zoster in Solid Organ Transplant Recipients Carrying Killer Cell Immunoglobulin-Like Receptor B Haplotypes

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Background. Natural killer cell function is regulated by inhibitory and activating killer cell immunoglobulin-like receptors (KIR). Previous studies have documented associations of KIR genotype with the risk of cytomegalovirus (CMV) replication after solid organ transplantation. **Methods.** In this study of 649 solid organ transplant recipients, followed prospectively for infectious disease events within the Swiss Transplant Cohort Study, we were interested to see if KIR genotype associated with virus infections other than CMV. **Result.** We found that KIR B haplotypes (which have previously been linked to protection from CMV replication) were associated with protection from varicella zoster virus infection (hazard ratio, 0.43; 95% confidence interval, 0.21-0.91; $P = 0.03$). No significant associations were detected regarding the risk of herpes simplex, Epstein-Barr virus or BK polyomavirus infections. **Conclusions.** In conclusion, these data provide evidence that the relative protection of KIR haplotype B from viral replication after solid organ transplantation may extend beyond CMV to other herpes viruses, such as varicella zoster virus and possibly Epstein-Barr virus.

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Natural killer (NK) cells are important in the early response against many pathogens including viruses. In contrast to B and T lymphocytes, they do not express rearranged surface receptors. Instead, diversity in the NK cell repertoire is a function of expression of varied combinations of inhibitory and activating surface receptors. It has been shown recently that

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thousands of different NK cell phenotypes exist within the polyclonal pool of healthy donor NK cells.[1]

Among the most polymorphic NK cell receptors are killer-cell immunoglobulin-like receptors (KIR). The KIR can be either activating or inhibitory in nature, depending on the structure of their intracellular tail containing an immunoreceptor tyrosine-based inhibitory or activating motif (immunoreceptor tyrosine-based inhibitory motif/immunoreceptor tyrosine-based activating motif).[2] Inhibitory KIR mediate NK cell tolerance by binding to self-HLA class I molecules. By contrast, the ligands and physiological relevance of activating KIRs are only poorly understood; binding to HLA class I has only been documented for KIR2DS1, KIR2DS2, and KIR2DS4.[3-5] The KIR genes segregate as haplotypes, which are classified as "A" if they contain a canonical set of six inhibitory receptors and 1 single activating KIR gene (KIR2DS4), whereas the remaining haplotypes, which may contain up to 5 additional activating receptors, are collectively classified as "B." In whites, A and B haplotypes are found at similar frequencies. Recipient B haplotype and high numbers of activating KIR genes have been linked with protection from cytomegalovirus replication after solid organ transplantation (SOT) in a number of studies.[6,7] More recently, several studies have suggested that KIR genes may also associate with the risk for other viral infections, such as hepatitis C,[8] herpes simplex,[9] BK polyomavirus (BKPyV),[10] and influenza.[11] For Epstein-Barr virus (EBV) and varicella zoster virus (VZV), 2 further members of the human herpes virus family, evidence for involvement of NK cells in disease control recently emerged, but no possible correlation with KIR genotype has been investigated yet.[12,13] For several of the above-mentioned viruses, different receptors were shown to be involved in the innate immune response.[14-16] At the same time, all these receptors are present in every individual. In contrast, KIR receptors vary in number and composition between individuals. A possible influence of single KIR receptors might therefore operate as a prognostic marker. As virus infection/replication is a frequent complication of immunosuppression after SOT, we were interested to analyze the correlation of KIR genotype and virus replication after SOT.

We made use of the Swiss Transplant Cohort Study, a large prospective multicenter effort collecting data and bio samples on all solid organ transplants performed in Switzerland,[17] to address whether recipient KIR genotype associates with the risk of viral infections in recipients of SOT.

PATIENTS AND MATERIALS

Patients

Six hundred forty-nine patients undergoing single SOT at 6 transplant centers in Switzerland between May 2008 and December 2010 were combined in this analysis (Inselspital Bern, n = 99; Centre Hospitalier Universitaire Vaudois, n = 102; Hôpitaux Universitaires de Genève, n = 95; Kantonsspital St. Gallen, n = 15; Universitätsspital Basel, n = 106; Universitätsspital Zürich, n = 232). Induction and maintenance immunosuppressive regimens in patients grouped by KIR haplotype are summarized in Table 1 along with demographic characteristics.

Data on transplant characteristics and transplant outcome including infectious complications were prospectively collected and retrieved using an electronic database.[17] Written informed consent was obtained from all study participants, and the study was approved by the institutional review boards in all centers.

TABLE 1.

Patient characteristics

KIR haplotype	AA (n = 176)		BX (n = 473)		P
Patient age at transplantation					
Median (range)	50	(1–75)	50	(0–79)	0.91
Sex (n, %)					
Male	116	(66)	309	(65)	0.89
Female	60	(34)	164	(35)	
Center (n, %)					
Basel	23	(13)	83	(18)	0.26
Bern	29	(17)	70	(15)	
Geneva	28	(16)	67	(14)	
Lausanne	36	(21)	66	(14)	
St. Gallen	4	(2)	11	(2)	
Zürich	56	(32)	176	(37)	
No. HLA-A/B/DR-mismatches (n, %)					
0-2	13	(7)	47	(10)	0.10
3-4	53	(30)	150	(32)	
5-6	94	(53)	208	(44)	
Missing	16	(9)	68	(14)	
Antibody induction (n, %)					
Anti-CD25 MAb	104	(59)	282	(60)	0.98
ATG	32	(18)	87	(18)	
None	40	(23)	62	(13)	
Maintenance immunosuppression (n, %)					
Tacrolimus	120	(68)	317	(67)	0.78
Cyclosporine	65	(37)	176	(37)	0.95
Prednisone	161	(92)	425	(90)	0.53
MMF	163	(93)	437	(92)	0.92
mTOR	22	(13)	62	(13)	0.84
Antiviral prophylaxis (n, %)					
Ganciclovir/valgancyclovir	68	(39)	179	(38)	0.85
Acyclovir/valacyclovir	23	(13)	36	(8)	0.03
Organ transplant (n, %)					
Heart	23	(31)	51	(69)	0.88
Kidney	78	(27)	213	(73)	
Liver	50	(27)	138	(73)	
Lung	25	(26)	71	(74)	

ATG indicates anti-thymocyte globulin; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin inhibitor (i.e., sirolimus or everolimus).

KIR Genotyping

The KIR genotyping was performed using a reverse sequence-specific oligonucleotide method (OneLambda, Canoga Park, CA) according to the manufacturer's instructions,[7] these results were in part reconfirmed by quantitative polymerase chain reaction (qPCR).[18] The KIR genotypes were grouped into AA if they contained only the canonical group A haplotype genes (KIR2DL1, KIR2DL3, KIR2DL4, KIR3DL1, KIR3DL2, KIR3DL3, and KIR2DS4). Any genotype containing additional KIR genes is referred to as a BX, as it contains at least 1 group B haplotype.[19] The BX patients were further subdivided into imputed BB haplotypes based on the absence of the A haplotype genes KIR2DL3, KIR2DL1 and KIR3DL1. Finally, genotypes were dichotomized into telomeric and centromeric A and B haplotype motifs according to published algorithms.[20]

TABLE 2.
Infection status patients and donors

KIR haplotype	AA (n = 176)		BX (n = 473)		*P*
EBV serology (n, %)					
D−/R−	2	(1)	5	(1)	0.95
D−/R+	7	(4)	26	(6)	
D+/R−	11	(6)	29	(6)	
D+/R+	145	(82)	387	(82)	
Missing	11	(6)	26	(6)	
HSV serology (n, %)					
D−/R−	3	(2)	16	(3)	0.22
D−/R+	14	(8)	19	(4)	
D+/R−	12	(7)	35	(7)	
D+/R+	50	(28)	150	(32)	
Missing	97	(55)	253	(54)	
VZV serology (n, %)					
D−/R−	3	(2)	2	(0)	0.33
D−/R+	10	(6)	24	(5)	
D+/R−	3	(2)	14	(3)	
D+/R+	77	(44)	198	(42)	
Missing	83	(47)	235	(50)	

Diagnosis of Viral Infections

Recipients of kidney transplants were screened for BKPyV replication by qPCR in blood and urine at minimum once every 3 months in the first year after transplantation. Additionally, BKPyV replication was assessed by qPCR when clinically indicated. Patients receiving organ transplants other than kidney were not regularly screened for BKPyV. The EBV screening guidelines differ between the involved study centers. In 121 patients, EBV replication was assessed 6 and 12 months after transplantation. The remaining patients were tested for EBV based on clinical suspicion. In both cases, EBV replication was detected by qPCR from the blood. Infection with herpes simplex virus (HSV) was diagnosed clinically and confirmed by qPCR only exceptionally in single cases. Infection with varicella zoster was clinically diagnosed in totally 28 patients. Of these, diagnosis was reassessed and confirmed by qPCR in 17 patients. The serological status for EBV, HSV, and VZV of donors and recipients before transplantation is indicated in Table 2.

Statistical Analysis

Patient characteristics were compared by Mann-Whitney *U* test or Pearson χ^2 test, where appropriate. The cumulative incidence of viral infection/replication events (± standard error) was estimated using death and graft loss as competing risks. Patients were grouped into those carrying 2 KIR A haplotypes (AA) versus those carrying 1 or 2 KIR B haplotypes (BX). Only the first episode of infection with each pathogen was considered in each patient. Cox regression was used for multivariable analyses, adjusting for induction immunosuppression, number of HLA mismatches (HLA-A/-B/-DR), graft rejection and respective therapy, type of organ transplanted, for recipient pretransplant serology, and antiviral prophylaxis (val-/ganciclovir and val-/acyclovir) in the case of herpes virus infections. All statistical analyses were performed with SPSS v.21 (IBM Corp, Armonk, NY).

RESULTS

The following numbers of infectious episodes were recorded in this cohort: cytomegalovirus, 289; EBV, 98; HSV, 69; BK virus (BKV), 63; rhinovirus, 32; hepatitis C virus, 29, VZV, 28; influenza virus, 20; respiratory syncytial virus, 16. Because viral infections of the respiratory tract are frequent, and only in a minority of cases identification of the pathogen responsible is attempted, we excluded rhinovirus, influenza virus, and respiratory syncytial virus from the analysis. Cytomegalovirus and hepatitis C virus were also excluded because the effect of KIR genotype on virus replication/infection has been described in previous studies.[6-8]

Analysis of the cumulative incidences of viral infections revealed that presence of a KIR-BX haplotype in the patient provided relative protection from VZV replication. The

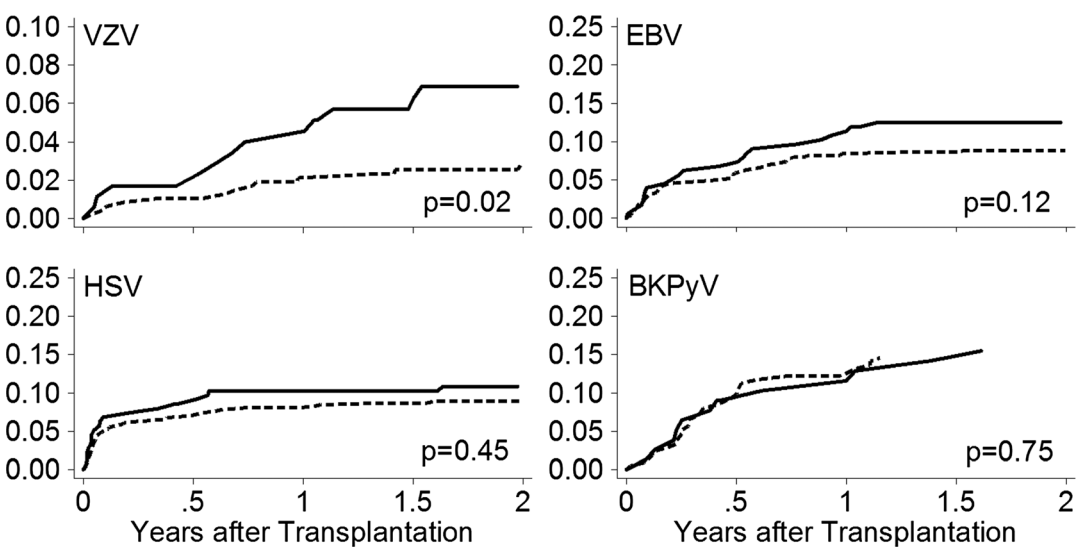

FIGURE 1. Cumulative incidence of varicella zoster (VZV), EBV, HSV, and BKPyV. Solid lines represent patients homozygous for the KIR-A haplotype (AA), whereas dashed lines represent patients carrying 1 or 2 KIR B haplotypes (BX). *P* value derived from Gray test.

2-year cumulative incidence of VZV infection was significantly lower in KIR-BX haplotype patients (3% ± 1%) compared to AA individuals (7% ± 2%, $P = 0.02$, Figure 1). A trend toward lower rates of EBV replication was also observed (2-year cumulative incidence 9% ± 1% versus 13% ± 3%); however, this difference did not reach the level of statistical significance ($P = 0.12$, Figure 1). For the remaining viruses, no effect of KIR haplotype was observed: HSV, 9% ± 1% versus 11% ± 2% ($P = 0.45$); and BKPyV, 15% ± 2% versus 15% ± 4% ($P = 0.75$, Figure 1) for BX and AA haplotype patients, respectively.

To further address the correlation of KIR haplotype and protection from VZV, we grouped patients by imputed haplotypes (AA versus AB versus BB) and by centromeric and telomeric KIR A and B motifs. This analysis revealed that protection from VZV reactivation was related to centromeric ($P = 0.05$) rather than telomeric ($P = 0.44$) KIR B motifs (Figure 2, upper and middle panels). Furthermore, we found that 1 haplotype B was associated with relative protection from VZV reactivation, as rates in AB and in BB patients were comparable (6% ± 2% versus 7% ± 3%, respectively, Figure 2, lower panel). Finally, multivariable analysis confirmed a statistically significant protective effect of KIR BX status regarding posttransplant VZV infection (hazard rate vs AA haplotype: 0.43, 95% confidence interval, 0.21-0.91; $P = 0.03$). Similarly, the risk for EBV replication after adjustment for covariates was reduced still without reaching the level of statistical significance (hazard ratio, 0.68; 95% confidence interval, 0.41-1.12; $P = 0.13$).

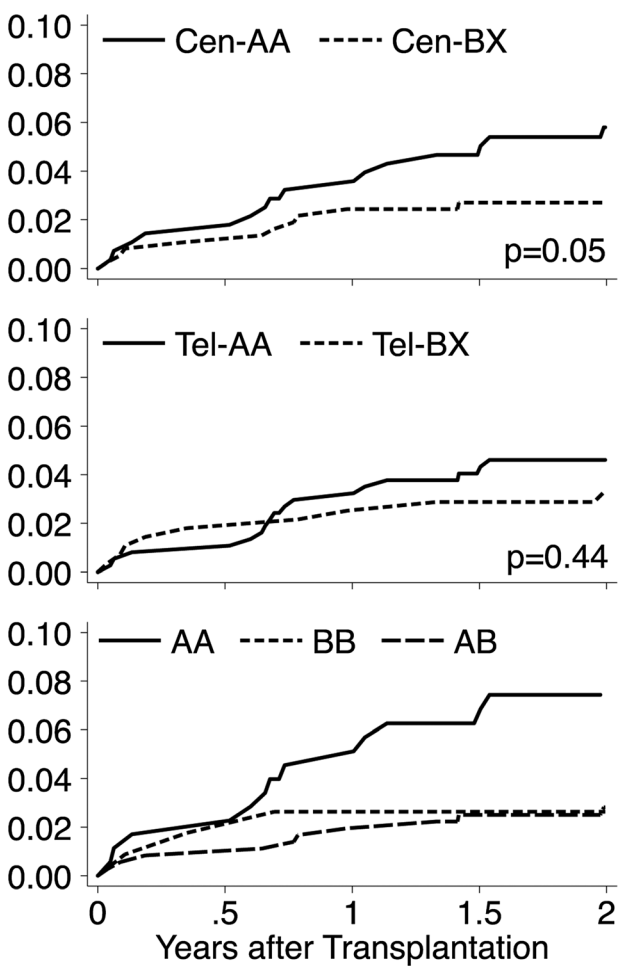

FIGURE 2. Cumulative incidence of VZV events in patients grouped by telomeric and centromeric KIR-B haplotype content (upper and middle panel) and by imputed haplotypes (lower panel). For the upper and middle panels, solid lines represent patients homozygous for the KIR-A haplotype (AA), whereas dashed lines represent patients carrying 1 or 2 KIR B haplotypes (BX). *P* value derived from Gray test.

DISCUSSION

In this study, we report that patients carrying KIR B haplotypes benefit from relative protection regarding VZV reactivation during the first 2 years after SOT. This effect appeared to be specifically linked to VZV as no effect was seen on HSV and BKV replication. The EBV replication was less frequent among carriers of B haplotypes, but this difference did not reach statistical significance, presumably in part due to the low rate of events for this type of complication. It is therefore notable that the data presented here suggest susceptibility to activating KIRs for 1 or possibly 2 further members of the herpes virus family besides cytomegalovirus (CMV). To further disclose which activating KIRs may be involved in immunological control of VZV, we divided activating KIRs in relation to KIR2DS4 as previously described in centromeric and telomeric genes.[20] These analyses illustrate that centromeric rather than telomeric KIR loci are associated with protection from VZV, reducing the number of potential candidate loci mainly to 3: the inhibitory KIR2DL2 and the activating receptors KIR2DS2 and KIR2DS3. KIR2DS3 is an unlikely candidate, as the most prevalent alleles are not expressed on the cell surface. Unfortunately, further genotype/phenotype correlations will add little to discriminate between the effect of these 2 genes, as they are in almost perfect linkage disequilibrium.[21] Another limitation of this study derives from the fact that diagnosis of viral replication was based on clinical suspicion for some of the viruses analyzed, implying that subclinical replication may have been missed in some instances.

Our findings stand in line with previous work exploring the physiological relevance of activating KIR. Several recent studies have described a protective effect of activating KIRs against CMV replication in different settings of immunosuppression.[6,7] After SOT or hematopoietic stem cell transplantation, when the adaptive immune system is pharmacologically suppressed, patients with a higher number of (haplotype B) activating KIR genes experience relative protection from CMV replication.[22,23] Further clinical conditions associated with KIR B haplotypes are reduced relapse rates in AML patients after allogeneic hematopoietic stem cell transplantation (if KIR B genes are present in the donor); and a reduced risk of preeclampsia in women carrying activating KIR genes.[24,25] These associations indicate that activating KIR receptors might recognize patterns on wide range of different potential target cells. We therefore explored the possibility that KIR haplotype associates with the susceptibility to other opportunistic infections in patients under pharmacological immunosuppression. Apart from CMV and hepatitis C,[6-8] limited knowledge regarding potential roles for KIR and NK cells in antiviral immunity exists. No effect of KIR haplotype was seen regarding replication of HSV and BKPyV, which stands somewhat in contradiction to previous studies partly done in healthy donors.[9,10] However, this may reflect the different role for NK cells in patients with compromised adaptive immunity

and the sites of reactivation. In summary, we find that telomeric B-haplotype KIR genes are associated with protection from VZV reactivation after SOT. If confirmed, these data may have an impact on VZV prophylaxis in these patients.

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