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Abstract: **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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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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L.S. analyzed the data and wrote the article. G.T. wrote the article. A.G. and K.S. performed the research and wrote of the article. H.H.H., C.G., C.vD., K.B., N.J.M., C.B., J.V., O.M., P.M., and C.H. analyzed data and wrote the article. M.S. designed the research, analyzed the data, and wrote the article.

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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,

TABLE 1.
Patient characteristics

| KIR haplotype | AA | | BX | | P |
|--------------------------------------|-----------|--------|-----------|--------|------|
| | (n = 176) | | (n = 473) | | |
| 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).

and the study was approved by the institutional review boards in all centers.

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 (\pm 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

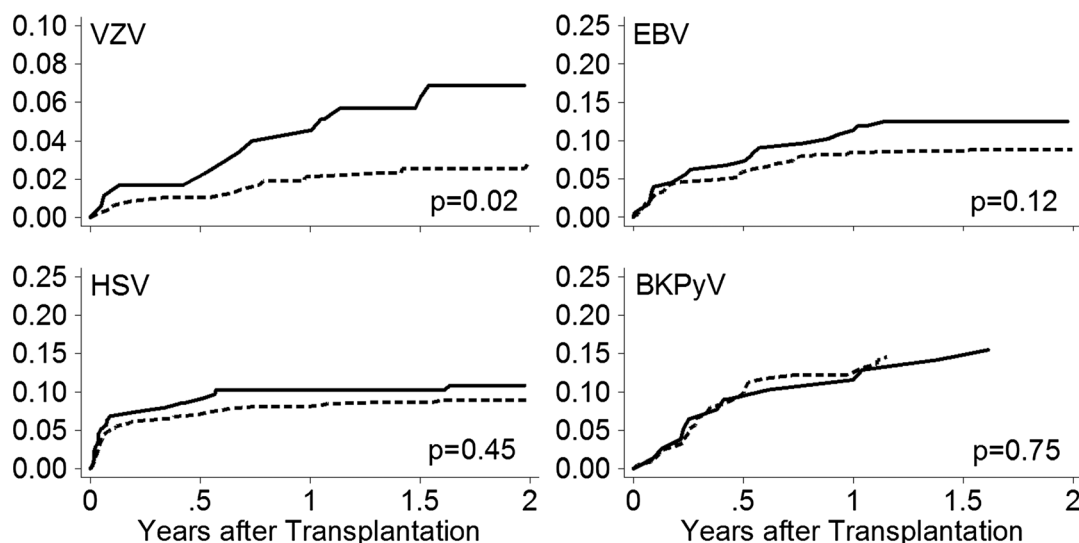


FIGURE 1. Cumulative incidence of varicella zoster (VZV), EBV, HSV, and BKPyV. Solid lines represent patients homozygous for the KIR-A haplotype (AA), whereas dashed lines represent patients carrying 1 or 2 KIR B haplotypes (BX). *P* value derived from Gray test.

2-year cumulative incidence of VZV infection was significantly lower in KIR-BX haplotype patients ($3\% \pm 1\%$) compared to AA individuals ($7\% \pm 2\%$, $P = 0.02$, Figure 1). A trend toward lower rates of EBV replication was also observed (2-year cumulative incidence $9\% \pm 1\%$ versus $13\% \pm 3\%$); 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, $9\% \pm 1\%$ versus $11\% \pm 2\%$ ($P = 0.45$); and BKPyV, $15\% \pm 2\%$ versus $15\% \pm 4\%$ ($P = 0.75$, 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 ($6\% \pm 2\%$ versus $7\% \pm 3\%$, respectively, Figure 2, lower panel). Finally, multivariable

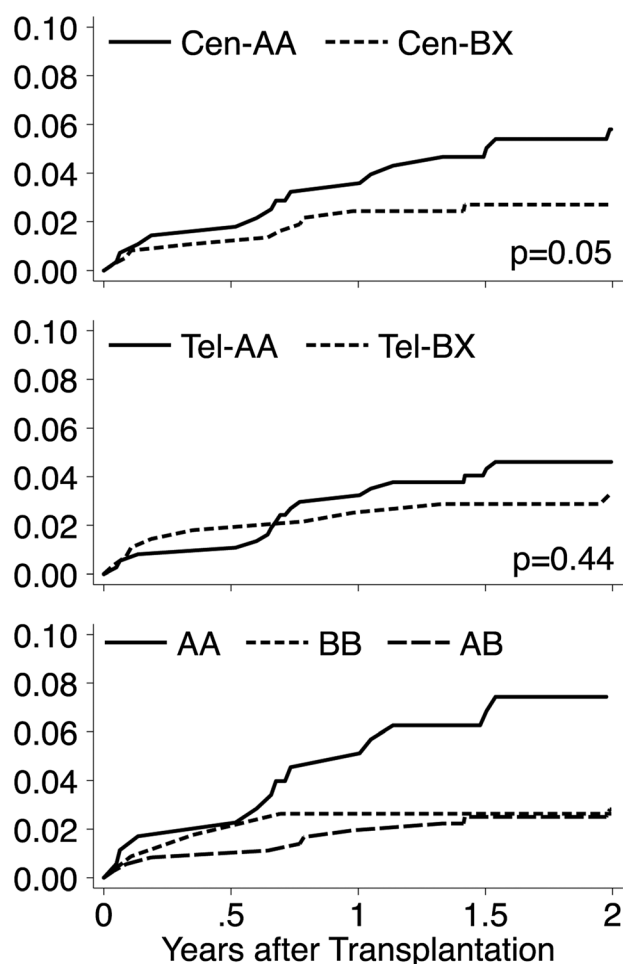


FIGURE 2. Cumulative incidence of VZV events in patients grouped by telomeric and centromeric KIR-B haplotype content (upper and middle panel) and by imputed haplotypes (lower panel). For the upper and middle panels, solid lines represent patients homozygous for the KIR-A haplotype (AA), whereas dashed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

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; $P = 0.13$).

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.

REFERENCES

- Horowitz A, Strauss-Albee DM, Leipold M, et al. Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. *Science translational medicine*. 2013;5:208ra145.
- Rajalingam R. Overview of the killer cell immunoglobulin-like receptor system. *Methods Mol Biol*. 2012;882:391.
- Stewart CA, Laugier-Anfossi F, Vely F, et al. Recognition of peptide-MHC class I complexes by activating killer immunoglobulin-like receptors. *Proc Natl Acad Sci U S A*. 2005;102:13224.
- Graef T, Moesta AK, Norman PJ, et al. KIR2DS4 is a product of gene conversion with KIR3DL2 that introduced specificity for HLA-A*11 while diminishing avidity for HLA-C. *J Exp Med*. 2009;206:2557.
- Liu J, Xiao Z, Ko HL, et al. Activating killer cell immunoglobulin-like receptor 2DS2 binds to HLA-A*11. *Proc Natl Acad Sci U S A*. 2014;111:2662.
- Hadaya K, de Rham C, Bandelier C, et al. Natural killer cell receptor repertoire and their ligands, and the risk of CMV infection after kidney transplantation. *Am J Transplant*. 2008;8:2674.
- Stern M, Elsasser H, Honger G, et al. The number of activating KIR genes inversely correlates with the rate of CMV infection/reactivation in kidney transplant recipients. *Am J Transplant*. 2008;8:1312.
- Khakoo SI, Thio CL, Martin MP, et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science*. 2004;305:872.
- Moraru M, Cisneros E, Gomez-Lozano N, et al. Host genetic factors in susceptibility to herpes simplex type 1 virus infection: contribution of polymorphic genes at the interface of innate and adaptive immunity. *J Immunol*. 2012;188:4412.
- Trydzenskaya H, Juerchott K, Lachmann N, et al. The genetic predisposition of natural killer cell to BK virus-associated nephropathy in renal transplant patients. *Kidney Int*. 2013.
- Aranda-Romo S, Garcia-Sepulveda CA, Comas-Garcia A, et al. Killer-cell immunoglobulin-like receptors (KIR) in severe A (H1N1) 2009 influenza infections. *Immunogenetics*. 2012;64:653.
- Chijioke O, Muller A, Feederle R, et al. Human natural killer cells prevent infectious mononucleosis features by targeting lytic Epstein-Barr virus infection. *Cell Rep*. 2013;5:1489.
- Orange JS. Natural killer cell deficiency. *J Allergy Clin Immunol*. 2013;132:515.
- Fiola S, Gosselin D, Takada K, et al. TLR9 contributes to the recognition of EBV by primary monocytes and plasmacytoid dendritic cells. *J Immunol*. 2010;185:3620.
- Ribeiro A, Wornle M, Motamedi N, et al. Activation of innate immune defense mechanisms contributes to polyomavirus BK-associated nephropathy. *Kidney Int*. 2012;81:100.
- Paludan SR, Bowie AG, Horan KA, et al. Recognition of herpesviruses by the innate immune system. *Nat Rev Immunol*. 2011;11:143.
- Koller MT, van Delden C, Muller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *Eur J Epidemiol*. 2013;28:347.
- Alves LG, Rajalingam R, Canavez F. A novel real-time PCR method for KIR genotyping. *Tissue Antigens*. 2009;73:188.
- Uhrberg M, Valiante NM, Shum BP, et al. Human diversity in killer cell inhibitory receptor genes. *Immunity*. 1997;7:753.
- Stern M, Hadaya K, Honger G, et al. Telomeric rather than centromeric activating KIR genes protect from cytomegalovirus infection after kidney transplantation. *Am J Transplant*. 2011;11:1302.
- Hsu KC, Chida S, Geraghty DE, et al. The killer cell immunoglobulin-like receptor (KIR) genomic region: gene-order, haplotypes and allelic polymorphism. *Immunol Rev*. 2002;190:40.
- Cook M, Briggs D, Craddock C, et al. Donor KIR genotype has a major influence on the rate of cytomegalovirus reactivation following T-cell replete stem cell transplantation. *Blood*. 2006;107:1230.
- Zaia JA, Sun JY, Gallez-Hawkins GM, et al. The effect of single and combined activating killer immunoglobulin-like receptor genotypes on cytomegalovirus infection and immunity after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:315.
- Cooley S, Weisdorf DJ, Guethlein LA, et al. Donor selection for natural killer cell receptor genes leads to superior survival after unrelated transplantation for acute myelogenous leukemia. *Blood*. 2010;116:2411.
- Xiong S, Sharkey AM, Kennedy PR, et al. Maternal uterine NK cell-activating receptor KIR2DS1 enhances placentation. *J Clin Invest*. 2013;123:4264.