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COMMENTARY
Host-Microbe Biology

mSphere of Influence: It's Not Me, It's You—How Donor Factors Influence Kidney Transplant Outcomes

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ABSTRACT Diana V. Pastrana works in the field of DNA tumor virus biology. In this mSphere of Influence article, she reflects on how the two papers "Donor origin of BKV replication after kidney transplantation" (C. Schmitt, L. Raggub, S. Linnenweber-Held, O. Adams, et al., J Clin Virol 59:120–125, 2014, https://doi.org/10.1016/j.jcv.2013.11.009) and "Neutralizing antibody-mediated response and risk of BK virus-associated nephropathy" (M. Solis, A. Velay, R. Porcher, P. Domingo-Calap, et al., J Am Soc Nephrol 29:326–334, 2018, https://doi.org/10.1681/ASN.2017050532) reminded her of the importance of allowing data, and not adherence to dogma, to drive her research.

KEYWORDS BKPyV, BKPyVAN, BKV, PVAN, kidney, polyomavirus, serology, transplant

The first successful kidney transplantation was performed in the 1950s between twin brothers. After that first procedure, complications arose in other patients due to immunological recognition of the transplanted organ resulting in rejection, prompting the introduction of immune suppression drugs as standard practice. Advances in these drugs have enabled countless patients with end-stage renal disease to improve their long-term survival and quality of life. These advances are not without drawbacks, however, as immune suppression allows some latent viral infections to resurge and, in some instances, threaten the viability of the transplanted organ. BK polyomavirus (BKPyV) infection is particularly common in this patient population and is associated with increased morbidity, often leading to kidney damage in the form of virus-associated nephropathy (BKPyVAN). The majority (>90%) of healthy adults are seropositive for BKPyV and can occasionally exhibit asymptomatic shedding of the virus in urine. Due to the ubiquity of BKPyV infections and high seropositivity rates, the scientists working in the transplantation field had long assumed that the BKPyVAN was primarily due to reactivation of latent virus in the recipient after the loss of cellular immunity. A few researchers (1–4) did recognize the viral and serological differences between the donor and the recipient, but this work was unable to shift the long-standing belief in donor-derived infections. Two recent papers suggest that it is not enough to monitor viruria and viremia in all patients equally but that there might be a subpopulation that is at greater risk for BKPyVAN, mainly due to inadequate immunity to the donor's BKPyV genotype. Consideration of donor factors (aside from histocompatibility markers) might have a great impact on the success of the transplants.

In the paper "Donor origin of BKV replication after kidney transplantation" by Schmitt et al. (5), the authors evaluated the presence of virus in urine from 249 donor and recipient pairs. Thirty-two donors were found to be shedding BKPyV prior to the transplant, and 20 of the paired recipients developed viruria posttransplantation. One of the strengths of that paper is that rather than merely looking for the presence or absence of BKPyV, the authors sequenced the PCR products in order to distinguish among viral genotypes and variants. This approach revealed that the BKPyV sequence isolated from the recipient posttransplantion was identical to that found in the donor. The authors elegantly demonstrated that this could not be coincidental. Analysis of

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sequences from GenBank as well as from unrelated donors showed that the probability of obtaining identical sequences in the donor and recipient was much lower in randomly assigned pairs from this theoretical population. Moreover, viruria data were available from two recipients prior to as well as after transplantation. Strikingly, the recipient sequences collected before and after transplantation were divergent, but the recipient posttransplant sequence was identical to that in the virus shed from the donor. Schmitt et al. also analyzed the serostatus of the donor and the recipient and found, as shown previously, that only a positive serostatus of the donor but not the recipient correlated with viral replication posttransplantion. The aggregate of data from that paper suggests that in many instances, rather than representing reactivation of the recipients' BKPyV, the virus originated from the donor, especially if the donor had high anti-BKPyV antibody titers and was actively shedding virus prior to transplantation.

In "Neutralizing antibody-mediated response and risk of BK virus-associated nephropathy" by Solis et al. (6), the authors followed 168 kidney transplant recipients and 69 donors and assessed development of viruria, viremia, and BKPyVAN. As in the paper by Schmitt et al., the authors examined donor and recipient strains and immunological status. At the commencement of transplantation, genotype-specific neutralizing antibodies were present at equal levels in patients that were positive or negative for BKPyV DNA in their blood or urine. However, 24 months following transplantation, those patients that became DNA positive developed higher neutralizing antibody titers targeting the BKPyV strain that was found to be actively replicating. If a recipient had low neutralizing titers against the donor's genotype, that recipient was at a significantly increased risk of developing viremia. Conversely, a rise in neutralizing antibodies in longitudinal observations coincided with a decrease in viral load. The authors determined that patients could be stratified into high-risk or low-risk groups for developing a replicating infection. Neutralizing antibodies below a 50% inhibitory concentration (IC_{50}) of 4 $\log_{10}$ against the donor strain were insufficient to prevent viremia and BKPyVAN, thus providing a new predictive marker for BKPyVAN. A lesser but nonetheless important point made in that study was that 3 of 5 recipients that had received rituximab (which targets B cells) developed BKPyVAN. The ability of T-cell responses to control BKPyV infections has been well studied and its importance recognized. The article by Solis et al., however, highlighted that in the context of immune suppression, the neutralizing humoral responses might have a more prominent role than previously thought. In response to the Solis publication, researchers at Chapel Hill (7) corresponded with the editor and highlighted their own work with newborn mice and mouse polyomavirus (MPyV) infections. The pups were challenged with MPyV and were protected by maternal antibodies if they were born from MPyV-exposed mothers but developed high levels of viremia and nephropathy if born from naive mothers.

A few years ago, the members of our laboratory stumbled into the polyomavirus field encumbered with our own set of naive assumptions. When our initial BKPyV serological results did not conform to the leading theories, we immediately assumed a technical error on our part. It took many months of confirmatory and orthogonal analyses to convince us to trust our data despite their incongruence with the cumulative literature, suggesting an alternative explanation. In both of the papers described here, the authors eschewed the long-held views on the origins of BKPyVAN and, by freeing themselves from dogma, created new avenues of research that might help kidney transplantation recipients. These insights reminded me of the importance of being open to the possibility that the experimental results that challenge the status quo might not be a technical fluke but rather might be the key to advancing the field.

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