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# Exposing the molecular machinery of BK polyomavirus

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## Summary

BK polyomavirus (BKV) is an opportunistic pathogen that poses a serious threat to organ transplant recipients. Hurdiss and colleagues' beautiful new high-resolution cryo-EM reconstruction of BKV provides a structural roadmap for the ongoing development of therapeutic antibodies and vaccines targeting this potentially deadly virus. The study also serves as a platform for exploring the basic biology of virion assembly and infectious entry.

Polyomaviruses are a remarkably successful family of non-enveloped DNA viruses that infect vertebrates. Serological studies, as well as more recent surveys of the human microbiome, suggest that practically all human beings harbor chronic infections with multiple human polyomavirus species (Dalianis and Hirsch, 2013). Although it is unclear whether these infections are associated with any noticeable symptoms in healthy subjects, it is well established that some human polyomaviruses cause disease in immunosuppressed individuals. In particular, BK polyomavirus (BKV) damages engrafted kidneys in up to 10% of renal transplant patients. At present, the only proven approach is to carefully monitor transplant recipients for the appearance BKV in the blood. BKV viremia above a certain threshold is generally addressed by reducing the level of immunosuppression (Hardinger et al., 2010). Although the partial restoration of immune function typically brings nascent BKV replication under control, it comes with increased risk of immune rejection of the engrafted organ. There are currently no antiviral agents with clear clinical utility against BKV.

In the past few years, there has been increasing interest in the possibility that BKV nephropathy might be prevented or treated using antibodies that neutralize various strains of the virus (Pastrana et al., 2012; Randhawa et al., 2015). Such antibodies could either be induced through vaccination or administered as recombinant monoclonals (mAbs). The first human mAbs capable of binding BKV virions were reported late last year (Jelcic et al., 2015). It is not yet clear whether the mAbs are capable of neutralizing the infectivity of BKV. In summary, there is a pressing clinical need to better understand the molecular biology of antibody-mediated neutralization of BKV.

In the current issue of Structure, Hurdiss and colleagues report their work using cryo-electron microscopy with computerized image reconstruction (cryo-EM) to investigate the solution structure of the BKV virion. In addition to providing basic structural information about this medically important virus, the study lays the groundwork for understanding antibody-based therapies and, conceivably, small molecule inhibitors of infection or assembly.

The new cryo-EM structures provide interesting fine-details about the structure of the mature virion. In particular, the reconstructions offer a new perspective on the biology of the two minor capsid proteins, VP2 and VP3. A distinctive feature of polyomaviruses, and their distant cousins the *Papillomaviridae*, is that the viral genome is fully decorated with host-derived histone proteins. This stands in marked contrast to other DNA virus families, which tend to package the viral DNA with virally encoded polybasic proteins or small cationic molecules. Hurdiss and colleagues' reconstructions reveal the existence of two nested shells of electron density near the inner surface of the virion. The spacing of these shells implies that a layer of disc-shaped histones lie flat against the inner surface of the virion. This is different from the solenoid-type structure typical of chromatin organization in cells. Importantly, the nested shells of density are not observed in virus-like particles that lack the viral minor capsid proteins. These intriguing findings provide clues about the poorly understood mechanisms through which the viral genome is taken up into the nascent virion. Specifically, Hurdiss and colleagues propose a model in which the minor capsid proteins serve as a bridge between the major capsid protein shell and the chromatinized viral DNA within.

Looking forward, these types of analyses will be important for understanding the structural differences between different BKV genotypes, some of which have been shown to engage different glycan receptors on the cell surface during the infectious entry process (Pastrana et al., 2013). Co-structures with mAbs that show BKV genotype-specific neutralization (Randhawa et al., 2009), broad cross-neutralization, or non-neutralizing mAbs will be key for guiding efforts to develop new therapies to protect patients against BKV nephropathy.

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