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Further Defining the Human Virome using NGS: Identification of *Redondoviridae*

Kristin Noell[1] **and Jay K. Kolls**[1,*]
[1]Departments of Pediatrics & Medicine, Center for Translational Research in Infection and Inflammation, Tulane University School of Medicine, New Orleans, LA, USA
*Correspondence: jkolls1@tulane.edu
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In this issue of *Cell Host & Microbe*, Abbas et al. (2019) uncover a previously undefined family of single-stranded DNA viruses, *Redondoviridae*, in human ororespiratory sites. The presence of *Redondoviridae* associates with critical illness such as respiratory failure and periodontitis, illustrating the power of metagenomics to define the human virome.

Viruses are infectious agents that replicate only inside living cells and have the ability to infect a variety of hosts. Viral infections are common and also challenging; however, patients who possess a compromised immune system, such as the young and the elderly, are hypersusceptible to infection. There has been a lot of discussion within the virology community regarding the best method to determine viral infectivity, pathogenicity, and effect on the host microbiome. Virologists use a variety of methods to gain understanding of infection, replication, pathogenicity, and, more recently, the evolution of the viral genome. Traditionally, scientists have relied on culture-based methods to isolate previously undefined viruses such as the SARS coronavirus (Wang et al., 2005), Zika virus (Coelho et al., 2017), and the Middle East Respiratory Syndrome (MERS) coronavirus (Chan et al., 2017). However, for many human pathogens, including fungi such as *Pneumocystis* and some viruses, culture-based systems have not been developed yet. Mucosal membranes serve as hubs for microbial exposure, including viruses. The microbiome is often referred to as the collective genome of microorganisms that reside in an environmental niche or organism. The recent development of next-generation sequencing (NGS) has allowed the use of a culture-independent mechanism to understand the microbiome, the metagenome, and the virome, and has allowed the detection of previously uncharacterized human pathogens. For example, DeRisi and colleagues have used combined RNA-seq and DNA-seq platforms, which allow for the concurrent profiling of the host transcriptome and actively transcribed microbes and the detection of RNA viruses (Langelier et al., 2018).

Respiratory viruses are one of the most common infections affecting the lung and are encountered from birth through adult life. Respiratory syncytial virus (RSV), for example, accounts for over 150,000 hospitalizations in the United States alone and has an economic cost of well over $1 billion, with a significant amount of that occurring in the elderly and in children under age 5 (Amand et al., 2018). Despite the impact of RSV, which typically causes a disease in children termed bronchiolitis due to inflammation in the small airways, up to 50% of bronchiolitis can be RSV negative. Some of this is due to similar viruses such as human metapneumovirus. However, with NGS available now, researchers have been using these unbiased omics techniques to find new components of the virome as well as to identify potential new pathogens.

In this issue of *Cell Host & Microbe*, Abbas et al. (2019) describe the identification

of an unstudied viral family that is localized in human ororespiratory sites using NGS technologies. Prior investigations of the human respiratory tract virome in health and disease yielded the identification of short sequence reads that had limited homology to a swine-associated, circular, Rep-encoding, single-stranded DNA (CRESS) virus which was found in bronchoalveolar lavage (BAL) fluid from human organ donors (Cheung et al., 2014; Abbas et al., 2017). Due to this limited homology to porcine CRESS viruses, Abbas et al. (2019) hypothesized that these reads may belong to a previously uncharacterized viral family. Using sample prep that enriched for small DNA viruses followed by unbiased contig assembly, the authors have identified and propose the establishment of a previously undefined viral family: *Redondoviridae*. Abbas et al. (2019) used sample preparation that enriched for virus-like particles followed by constructing shotgun DNA libraries and metagenomic sequencing. This resulted in the identification of circular contigs of 3,000 base pairs. These were confirmed by Sanger sequencing, and they were able to construct two circular genomes. Additional analysis of human lung samples resulted in 19 complete genomes. Importantly, the authors did not find these genomes in reagents or as contaminates in washes from bronchoscopes that were used to collect some of these samples. The genomic data suggest these viruses are of eukaryotic origin, as they lack key features of phage for infection and replication in prokaryotes. Similar to other small ssDNA viruses, like adeno-associated virus, these viruses contain Rep and Cp (capsid) genes. The Rep protein is consistent with other small DNA and RNA viruses, as it contains two domains involved in rolling circle replication as well as helicase domain. Interestingly, the Cp genes were highly conserved, which may suggest that this viral family may not be under significant immunologic pressure to mutate. Taken together the genomic data suggest that redondoviruses are eukaryotic viruses. To establish a production infection, adeno-associated viruses (AAVs) require a helper virus such as adenovirus for replication. Analyses of 173 metagenomic samples revealed a highly statistical association between the presence of redondoviruses and members of the *Anelloviridae* family, another recently discovered viral family that is prevalent in humans but has not yet been associated with disease. In fact, redondoviruses were the second most abundant virus in these samples, after *Anelloviridae*. However, given that *Anelloviridae* are also small ssDNA viruses, it is unlikely that these viruses are help viruses.

Since the initial identification of the virus came from the lung, the authors queried for the presence of redondoviruses in other human samples. The authors found a high prevalence in patients with critical illness from both oropharyngeal samples, as well as in four samples taken from the lung of intubated patients. Additionally, the authors found a high prevalence in subjects with periodontal disease, and the viral burden decreased after treatment for periodontitis. How these ssDNA viruses affect disease is unclear. Given the known role of bacteria in periodontal disease though, one could postulate that a viral-bacterial interaction may play a role in pathogenesis. For example, viral infection of the airway can enhance bacterial biofilm formation (Kiedrowski and Bomberger, 2018), and there is a well-known association of influenza infection with secondary bacterial pneumonia (Robinson et al., 2015). The current study does not address Koch's postulates in terms of the role of redondoviruses in human disease, but with the identification of this previously uncharacterized family of viruses, additional studies will shed light on the role of these viruses in human health and disease.

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