Minireview

New evolutionary frontiers from unusual virus genomes
Christopher Desjardins, Jonathan A Eisen and Vishvanath Nene

Address: The Institute for Genomic Research, 9712 Medical Center Drive, Rockville, MD 20854, USA.

Correspondence: Vishvanath Nene. E-mail: nene@tigr.org. Jonathan Eisen. E-mail: jeisen@tigr.org

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Abstract

The sequences of two giant viral genomes, Mimivirus and a polydnavirus, have recently been published. Mimivirus has the largest known viral genome and encodes an unprecedented number of proteins, whereas the polydnavirus genome has an extremely low coding density and does not encode DNA-replication proteins. These and other unusual features challenge the way we view the evolution and definition of viruses.

If an alien landed on Earth and studied the biology here, it might justifiably conclude that viruses run the planet. They are numerically the most abundant biological entities [1], and they are profoundly important in shaping the ecology and evolution of just about every species on Earth [2]. Yet viruses are not considered to be alive by most biologists, and they have arguably fallen by the wayside in the genomics revolution [3]. The recent publication of the genome sequences of two unusual viruses, however, highlights the wealth of information that remains to be discovered through viral genomics. Here, we discuss Mimivirus [4] and Cotesia congregata Bracovirus [5] (CcBV) and the interesting questions they raise concerning the biology and evolution of viruses.

Both Mimivirus and CcBV are classified as double-stranded DNA (dsDNA) viruses, and some of their features are summarized in Table 1. Mimivirus was discovered in amoebae [6], and it has a cycle of viral transmission and replication that is typical of many dsDNA viruses (Figure 1a). Its name is derived from 'mimicking microbe,' in reference to the bacterium-like appearance of its large particle (400 nm in diameter) and its Gram-positive staining. Mimivirus has the largest known viral genome (1.18 megabase-pairs) and encodes an unprecedented number of components of the transcriptional, translational and replication machinery, many of which have not previously been identified in viruses [4]. In addition, the genome encodes a large number of genes associated with metabolic pathways. Although the size and content of the Mimivirus genome might rival those of some obligate intracellular prokaryotes, it still appears to be absolutely dependent on its host cell for synthesis of proteins.

CcBV differs from Mimivirus and other viruses in many fundamental aspects. As a member of the Polydnaviridae, the transmission and replication cycle of this Bracovirus is unconventional [7]. The Polydnaviridae - pronounced poly-d-na-viridae by the research community and named after the unique segmented structure of the packaged genome - consists of two subgroups, Bracoviruses and Ichnoviruses, which associate with braconid and ichneumonid wasps, respectively [7]. These wasps are parasitoids (parasites that kill their hosts) that attack caterpillars and are of particular interest for their use as biological control agents. In the wasp host, polydnaviruses exist in a benign state, integrated into the wasp genome as a provirus. Amplification of segments from the provirus and production of virions (particles containing viral DNA encased within a capsid) occurs only in the ovaries of a female wasp, and virions are co-injected with eggs during parasitization of caterpillars. The viral particles are replication-deficient in both hosts; the virus can increase in number only through genome amplification in wasp ovaries but is transmitted from wasp to wasp by vertical transmission of the provirus. Viral gene expression in caterpillars interferes with the latter's immune response and developmental cycle, promoting
Mimivirus is the sole member of Mimiviridae and is classified as a nucleocytoplasmic large DNA virus (NCLDV) [6] on the basis of the presence/absence pattern of 'core' genes defined for NCLDVs [8]. By contrast, the viral origins of polydnaviruses are less certain. It has been hypothesized from virion morphology that bracoviruses may be related to baculoviruses [7,9], but only three genes in the CcBV genome are similar to genes found in free-replicating viruses, two to a baculovirus and one to an ascovirus [5]. Thus, even though we have a genome sequence the origin of bracoviruses remains unclear. Many genes that are typical of viruses are absent from the CcBV genome and may have been transferred to the wasp genome, as is the case for a gene coding for a major structural protein in Campoletis sonorensis Ichnovirus [10].

Inferring viral phylogenies is often difficult, as high rates of viral evolution make it difficult to identify conserved genes between viruses. The ultimate origin of viruses - where viruses should be placed on the Tree of Life [11] - is even more vexing. Many theories abound [2,12-14]: that they evolved from a bacterial parasite, their gene content should overlap very little, if at all, with that of bacteria, archaea and eukaryotes. In contrast, if viruses evolved from a bacterial parasite, their content should resemble bacteria more than that of archaea and their genes should branch in evolutionary trees with genes from bacteria, as is the case for organelles [15].

But there are several complications in determining viral origins. First, it is possible that different types of viruses arose independently. Second, and more confounding, there has unquestionably been gene flow between viruses and their hosts, which means that any one gene might not reflect the phylogeny of the virus itself. The authors of the Mimivirus genome sequence paper [4] try to address this by making a concatenated alignment of multiple genes shared by Mimivirus and living organisms. They report that the viral genes branch as a sister group to the eukaryotes, potentially identifying Mimivirus as the basal member of a major branch on the Tree of Life. But in a separate phylogenetic analysis of the RNA polymerase β' subunit (one of the proteins used in the concatenated analysis and also encoded in other NCLDVs), Mimivirus did not group with the NCLDVs. The ramifications of this conflict are still unclear: is Mimivirus an NCLDV that acquired many of its genes through lateral transfer, although differences in codon usage between viruses and amoebae would indicate otherwise? Is it a sister-group to the eukaryotes and not an NCLDV, despite the presence of NCLDV core genes? Resolving such questions will have to wait until other members or close relatives of Mimiviridae are discovered and their genome sequences analyzed.
propose that bracoviruses may have evolved from mobile DNA that acquired the ability to be packaged into capsids (perhaps from a virus); the existence of remnants of transpo son and retrovirus-like elements in the CcBV genome provides additional support for such an argument. Genome sequencing and phylogenetic analysis of additional polydnaviruses, their proviral sequences, and genes associated with virion formation will be required to shed light on the question of whether bracoviruses are the product of reductive viral evolution or not.

Mimivirus expands our definition of viruses quantitatively to accommodate bigger genomes and larger particle size. Although Raoult et al. [4] point out that Mimivirus has more components of the cellular machinery than any other virus, in our opinion it does not yet seem to stretch the definition of viruses in any fundamental way. It is just a more complicated virus. By contrast, CcBV appears to differ qualitatively from many definitions of a virus (Table 1), but it could still be classified as a highly defective one. Clearly, these two viruses present some interesting problems regarding viral phylogeny and classification that remain to be resolved. Considering the importance of viruses in evolution, we believe that we need to direct more effort to systematically characterize the genomes and biology of diverse viruses, as this will further our understanding of how and where they fit into the Tree of Life [11].

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As CcBV has very few features associated with other viruses, and its coding content and gene structure resemble that of the wasp host more than that of viruses, Espagne et al. [5] raise questions about the viral ancestry of bracoviruses. They