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Genome chromatinization in giant double-stranded DNA viruses

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Giant viruses have extravagantly large double-stranded (ds)DNA genomes that are packaged into exceedingly complex virions. In two recent papers, Liu *et al.* and Valencia-Sánchez, Abini-Agbomson *et al.* show that some giant viruses encode unique histone doublets, which form nucleosomes remarkably similar to those found across the eukaryotic domain of life.

Keywords: viral genome packaging, icosahedral capsid, virus evolution, chromatin, family *Marseilleviridae*, phylum *Nucleocytoviricota* (NCLDV)

Virions (virus particles or capsids) represent metastable containers which protect the viral genetic information in hostile extracellular environments and facilitate its delivery into the host cell. However, the internal volume of spherical (typically icosahedral) capsids is limited and the viral genome would simply not fit inside without being compacted. Over billions of years, viruses have evolved multiple mechanisms of genome compaction and packaging. The smallest and simplest single-stranded RNA viruses knit their icosahedral capsids through protein-protein and protein-RNA interactions, compacting the genome in the process [1]. A very different strategy is used by most double-stranded (ds)DNA viruses, including tailed bacteriophages and herpesviruses, which use powerful ATP-driven motors, genome packaging ATPases, to pump the genomic DNA into preformed empty capsids, achieving near-crystalline packaging densities [2].

Another solution used by some viruses (and all cellular organisms) relies on chromatinization of the genome, i.e., the genome is condensed by chromatin proteins. Some viruses (e.g., adenoviruses) encode their own chromatin

proteins unrelated to the cellular counterparts, whereas others appropriate the chromatin proteins of their hosts. For instance, the circular dsDNA genomes of papillomaviruses and polyomaviruses are complexed with host-derived histones [3], the major chromatin proteins in eukaryotes and many archaea, which act as spools around which DNA wraps to create structural units called nucleosomes. The eukaryotic nucleosome invariably includes two copies of each of the four histones, H2A, H2B, H3, and H4, with H2B-H2A and H4-H3 forming heterodimers that assemble into an octamer that wraps ~147 bp of dsDNA to form nucleosomes. Strikingly, some viruses with giant icosahedral capsids and dsDNA genomes, namely, members of the families *Marseilleviridae* and '*Medusaviridae*', encode the entire complement of the core eukaryotic histones. Whereas in medusaviruses each histone homolog is encoded as a standalone protein [4] (just like in eukaryotes), in marseilleviruses, the four histones are encoded by just two genes in the form of unique histone doublets, vH2B-vH2A and vH4-vH3 [5, 6]. Although the existence of viral histone genes was known for over a decade, their function remained speculative. Now, two recent studies simultaneously published by Liu

et al [7] and Valencia-Sánchez, Abini-Agbomson *et al* [8] illuminate the role of viral histones in condensation of the giant viral genomes.

Liu *et al* [7] and Valencia-Sánchez, Abini-Agbomson *et al* [8] have determined the structures of nucleosomes formed by histone doublets of two different amoeba-infecting marseilleviruses, Melbournevirus and Marseillevirus, respectively. It turned out that the viral nucleosomes and the constituent histone doublets are remarkably similar to the canonical eukaryotic counterparts (Fig. 1A). Interestingly, however, the viral nucleosomes wrap less DNA compared to the eukaryotic ones (~120 bp versus ~147 bp, respectively), although the main contacts between the histones and DNA, including the basic amino acids defining the path for the DNA, are conserved between viral and eukaryotic histones. Furthermore, the viral nucleosomes are prone to dissociation and appear to be considerably less stable than the eukaryotic nucleosomes, a property attributed to reduced positive charge and distinct structural makeup of the viral histone subunits [7]. In eukaryotes, chromatin condensation and accessibility to RNA polymerase are primarily regulated by post-translational modifications on extended, positively charged N-terminal histone tails, especially those of H4 and H3. The tails of the viral histones do not appear to have the same function and instead assume structural roles; in the case of vH4, the N-terminal tail, instead of extending over the DNA, takes the opposite direction to interact with the core domain of vH4 [7, 8]. These changes likely further contribute to the lability of the viral nucleosomes. It has been suggested that metastability is an intrinsic property of viral nucleosomes, presumably facilitating timely transcription of the early viral genes by the host RNA polymerase recruited to the viral factory from the nucleus, thereby alleviating the need for ATP-dependent chromatin remodelers used by eukaryotes [7].

Viral histones have been detected in virus particles, suggesting that nucleosomes observed *in vitro* are also present within the virions [6, 7]. Importantly, Liu *et al* demonstrated that viral histones are important for viral

infectivity, with knockout of either viral histone doublet gene being associated with a strong fitness cost to the virus and loss of the mutant viruses after 2 days of propagation [7]. Expression of the GFP-tagged viral histones revealed their recruitment to the viral factories in infected cells, whereas in the absence of infection they were evenly distributed throughout the cell, suggesting that that chromatinization of the viral genome is a spatially orchestrated process. One of the outstanding questions is how marseilleviruses package their genomes into icosahedral capsids. Similar to other members of the realm *Varidnaviria*, marseilleviruses encode a putative genome packaging ATPase [6]. In the case of viruses for which the function of this protein has been investigated, it has been shown to play a key role during genome packaging into preformed capsids (e.g., in tectiviruses) or capsid intermediates (e.g., in poxviruses). However, this molecular motor is unlikely to promote the translocation of chromatinized substrates. One possibility is that nucleosomes are formed following the packaging of naked viral DNA into preformed histone-containing capsids. Indeed, empty marseillevirus particles have been observed in infected cells (e.g., [5]).

Another intriguing question is the provenance of the viral histones. Phylogenetic analyses consistently place the four (after splitting the doublets) groups of viral histones either as sister groups to or at the base of the corresponding eukaryotic core histones, whereas archaeal histones are more divergent and occupy the basal position in the trees (Fig. 1B) [4, 5, 8]. This topology suggests either viral origin of the eukaryotic histones or at least ancient divergence of the eukaryotic and viral histones, predating the last eukaryotic common ancestor. The idea that such key proteins as histones could have been acquired by eukaryal ancestor from viruses might appear heretic. However, it is known that in dinoflagellates, a group of single-celled eukaryotes, histones have been replaced by a chromatin protein from giant dsDNA viruses of the *Phycodnaviridae* family, which are evolutionarily related to marseilleviruses [9]. Furthermore, it has been suggested that at least one of the eukaryotic RNA polymerases has

been horizontally acquired from giant viruses [10]. Thus, the viral origin of eukaryotic histones should not be dismissed lightly (Fig. 1B). Finally, the fact that most other giant viruses do not encode histones begs the question of how their genomes are condensed and packaged. Further exploration of virus diversity and evolution,

coupled with structural and functional studies, such as those by Liu *et al* [7] and Valencia-Sánchez, Abini-Agbomson *et al* [8], are bound to uncover more surprises and clarify the extent of the giant virus contribution to the origin and evolution of eukaryotes.

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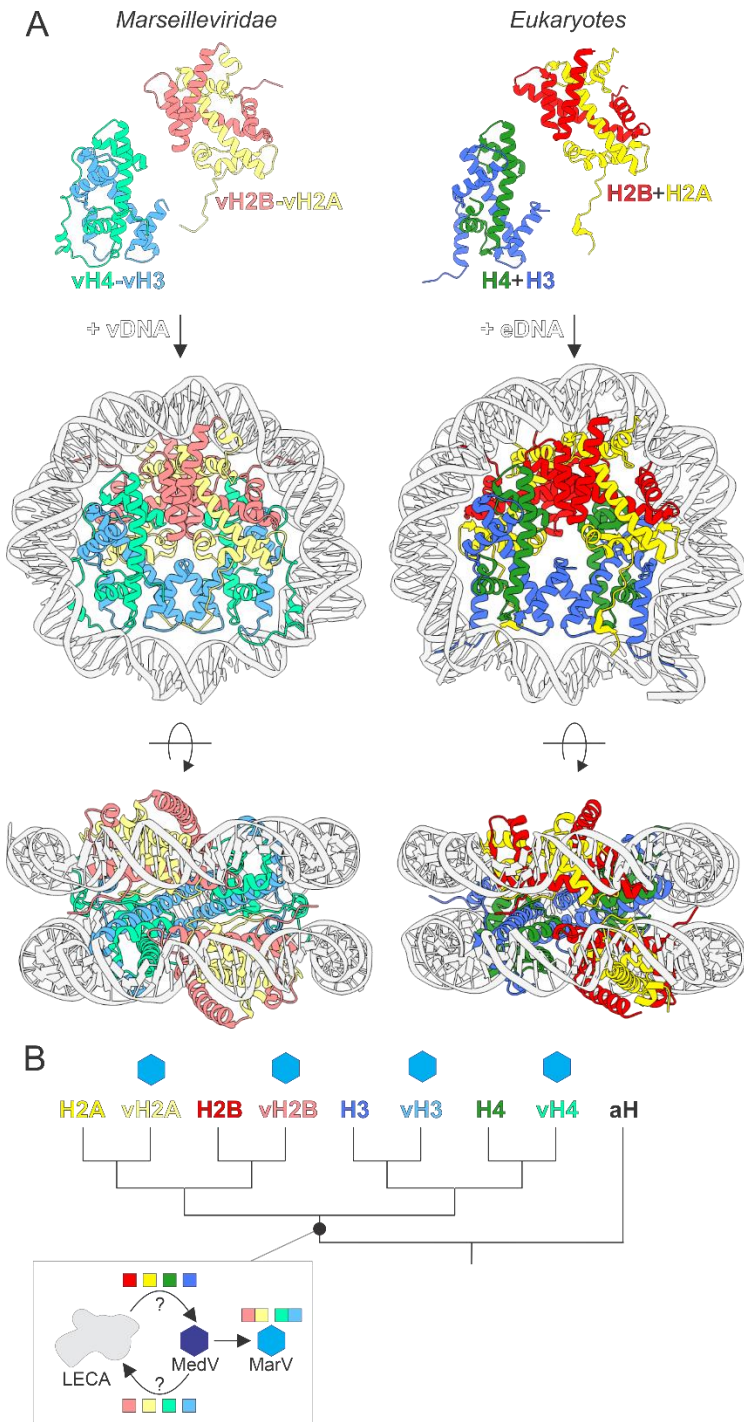


Figure 1. Genome chromatinization in giant viruses and their cellular hosts. **A.** Comparison of the vH2B-vH2A and vH4-vH3 histone doublets (top) and nucleosomes (middle and bottom) of Melbournevirus (left) with the corresponding eukaryotic counterparts (right). Each histone protein, depicted using ribbon representation, is colored differently. The shown histone structures have the following PDB accession numbers: 7n8n (Melbournevirus) and 7lz0 (*Xenopus laevis*). **B.** Schematic phylogeny showing the relationships between cellular and viral histones. Based on [4, 5, 8]. Branches corresponding to the viral histones are indicated with blue hexagons. The inset shows the alternative evolutionary scenarios whereby the histone genes (colored squares) are horizontally transferred between cells and viruses, possibly resembling contemporary medusaviruses (with the question marks indicating that the direction of transfer remains unclear). The viral histone genes are fused in one of the viral lineages to produce histone doublets found in marseilleviruses. Abbreviations: a, archaeal; e, eukaryotic; v, viral; LECA, last eukaryotic common ancestor; MarV, marseillevirus; MedV, medusavirus.