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Giant viruses and the origin of modern eukaryotes

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Several authors have suggested that viruses from the NucleoCytoplasmic Large DNA Viruses group (NCLDV) have played an important role in the origin of modern eukaryotes. Notably, the viral eukaryogenesis theory posits that the nucleus originated from an ancient NCLDV-related virus. Focusing on the viral factory instead of the virion adds credit to this hypothesis, but also suggests alternative scenarios. Beside a role in the emergence of the nucleus, ancient NCLDV may have provided new genes and/or chromosomes to the proto-eukaryotic lineage. Phylogenetic analyses suggest that NCLDV informational proteins, related to those of Archaea and Eukarya, were either recruited by ancient NCLDV from proto-eukaryotes and/or transferred to proto-eukaryotes, in agreement with the antiquity of NCLDV and their possible role in eukaryogenesis.

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Introduction

The discovery of giant viruses at the beginning of this century has sent a shock wave among evolutionists, triggering controversies about their nature and origin [1]. Amazingly, the discovery of *Mimivirus* [2] occurred only two years after two scientists independently suggested that the eukaryotic nucleus originated from a large DNA virus resembling poxviruses (the viral eukaryogenesis theory) [3,4]. Not surprisingly, most evolutionists did not take this theory seriously, since '*viruses are no part of the modern synthesis or more generally the traditional narrative of evolutionary biology*' [5]. Furthermore, the drastic switch from a viral particle (even big) to a nucleus (Figure 1a) may be hard to conceive, considering their very different nature and the number of events (gain/loss of traits) that would be required. However, this interpretation is typical of the virus/virion paradigm that conflates viruses and their virions [1,6,7•]. The study of *Mimivirus* has suggested considering the viral eukaryogenesis theory from a new perspective — that of the infected cell (or virocell, *sensu* Forterre [1,7•]) by revealing that this virus produces a giant viral factory (VF) whose size is similar to that of the nucleus [8]. The *Mimivirus* VF could thus be viewed as the nucleus of a *Mimivirus* virocell [1]. Accordingly, rather than figuring a virion being transformed into a nucleus, one could imagine that the VF of some ancient giant virus was at the origin of the nucleus (Figure 1b).

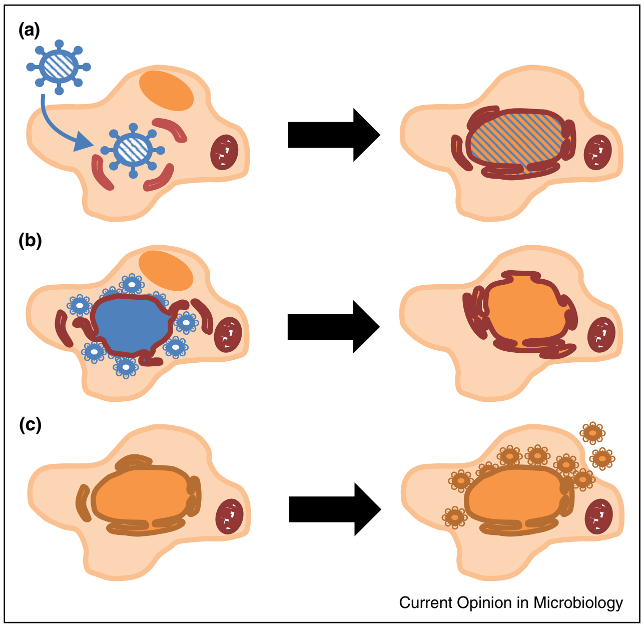
An evolutionary connection between the eukaryotic nucleus and viral factories

Most eukaryotic viruses (either RNA or DNA viruses) that replicate in the cytoplasm produce VFs that are sometimes called 'mininuclei' or 'nuclear-like organelles' [9,10,11••]. There are striking analogies between VF and the cell nucleus: they both function in the cytoplasm and many VFs recruit part of the endoplasmic reticulum membrane either to manufacture their own membrane and/or to build the internal membrane of their virions. The VFs of some NCLDV also typically assemble close to the microtubule organising center involved in nuclear mitosis [9]. Strikingly, Kuznetsov and co-workers have recently shown by atomic force microscopy that *Mimivirus* VFs are formed by the fusion of membrane vesicles that originated from invagination of the nuclear membrane [12••]. Even more fascinating, pandoraviruses and molliviruses invade and use the nucleus as VFs, recycling the nuclear membrane to build the internal membrane of their virions [13•]. It is tempting to imagine that these physiological connections recapitulate an ancient evolutionary pathway.

For instance, a first hypothesis could be that the nucleus originated from the VF of an ancient NCLDV that lived in a carrier state (a ribovirocell, *sensu* Forterre [1]) in a proto-eukaryotic cell (i.e. a cell producing ribosomes typical of the eukaryotic lineage). In that scenario, the genome of the persistent virus should have at some point fused with the genome of the proto-eukaryotic host and lost the capacity to produce virions, the newly formed genome permanently enclosed in a primitive nucleus derived from the ancient VF (Figure 1b).

An alternative scenario that links the eukaryotic nucleus and giant viruses was proposed by Claverie, who put the viral eukaryogenesis theory upside down by suggesting that some giant viruses originated from the nuclei of ancient proto-eukaryotic cells [6]. Envision a cellular nucleus acquiring the characteristics of a virion seems nonetheless hard. However, one could imagine that a nucleus of proto-eukaryotes evolved into a viral factory

Figure 1



Representations of different hypotheses for the viral eukaryogenesis theory. **(a)** The nucleus originated from a virion, perhaps after a fusion with a protonucleus (adapted from Figure 7.12, p 232 in [61]). **(b)** The nucleus of the cell derived from a viral factory and a protonucleus, or the cell recruited from a viral factory the traits required to manufacture a nucleus. **(c)** A cell nucleus evolved into a viral factory after acquiring the ability to produce virions.

after having gained and selected the genes responsible of virions production (Figure 1c). The problem would then be that such virion should have been immediately large enough to encapsulate a large chromosome, which might seem quite odd. Particularly, it has been suggested that large and complex virions most likely evolved from smaller and simpler ones [14•].

A third hypothesis linking the eukaryotic nucleus and the VF of NCLDV was proposed by Forterre and Prangishvili, who suggested that proto-eukaryotic cells may have obtained from ancient viruses they were interacting with, the ability to manufacture a nucleus — mimicking a VF — as a protective device against viruses [15] (Figure 1b). VFs indeed provide viruses with safe homes, having the transcription and replication of their genomes sheltered from cellular defences [9]. Similarly, the emergence of the nucleus might have provided proto-eukaryotes a way to transcribe and replicate their genomes sheltered from viral attack, a trait that would have been selected through evolution. In such scenario, eukaryotic viruses first replicated exclusively in the cytoplasm, until the ability to bypass this newly acquired cell defence (and hence to replicate in the nucleus) was acquired by some and represented an advantage that has spread to most of today's viruses.

Obviously, it will be difficult to test the validity of all these hypotheses, but they can nonetheless stimulate virologists to study in detail the architecture and physiology of VFs made by the diverse families of NCLDV. Preliminary analyses have shown that these VFs can be very diverse [13•] and hopefully further exploration of this diversity will reveal new unexpected connections with the eukaryotic nucleus.

All the above scenarios assume that the eukaryotic nucleus originated in 'proto-eukaryotes'. Some authors dismiss the existence of '*a proto-eukaryotic lineage independent of bacteria and archaea*' because they believe that modern eukaryotes originated directly from the association of an archaeon and a bacterium [16]. This association scenario has been strongly criticized by one of us (and others) from the viewpoint of biological plausibility (see [17,18] and references therein). However, the association scenario itself implies the existence of proto-eukaryotes, considering the many evolutionary innovations that should have taken place between the first eukaryote with a proto-mitochondrion (a complex archaeon in most association hypotheses) and LECA, the Last Eukaryotic Common Ancestor. These evolutionary innovations, hallmark of Eukaryotes, include for instance the formation of the nucleus, the emergence of the spliceosome, and the development of mitosis and meiosis [19•,20]. This represents plenty of time for NCLDV to originate and co-evolve with proto-eukaryotes and be involved in eukaryogenesis (see [21••] for a possible scenario of NCLDV origin in the framework of the association hypothesis) (Figure 2a). According to Woese's tree of life, NCLDV had even more time to co-evolve with proto-eukaryotes, since they could have originated in the whole branch of the universal tree leading from LUCA (the Last Universal Common Ancestor) to LECA, either before or after the split between Archaea and Eukarya (Figure 2b). In both cases, it is assumed that NCLDV originated before LECA. This is reasonable, considering that NCLDV are widespread today in various eukaryotic phyla [22].

NCLDV and the origin of eukaryotic proteins

Since modern NCLDV can integrate into eukaryotic genomes [23,24••], it is likely that integration of ancient NCLDV also occurred into proto-eukaryotic genomes. Accordingly, beside their possible involvement in the origin of the nucleus, NCLDV may have played a role in the origin of modern eukaryotes by introducing new genes (thus possibly new functions) in proto-eukaryotes. These proteins would have now usually lost all similarities with those of modern NCLDV, preventing the easy identification of their viral origin. A possible trace of this origin could be the fact that the proteome of eukaryotes and viruses are both strongly enriched in disordered proteins compared to the proteomes of Archaea and Bacteria [25]. Such proteins are probably especially important in viruses