Reasons to include viruses in the tree of life

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We read with interest the recent article in *Nature Reviews Microbiology* by Moreira and López-García (Ten reasons to exclude viruses from the tree of life. *Nature Rev. Microbiol.* 7, 306–311 (2009))¹ who courageously attempted to exclude viruses from the tree of life. The inability of viruses to self-sustain and self-replicate, their phylogenetic diversity, the origin of their cell-like genes and the instability of their genomes over time were emphasized to strengthen the argument. However, as discussed in this Correspondence, we emphasize that although we might be able to call viruses 'pseudo living entities' or 'molecular parasites' we cannot deprive them of their status as living entities.

We cannot compare primitive organisms such as viruses with complex living entities such as plants and animals. In fact, because viruses are 'mono-unitary' organisms, the most plausible comparison would be with animal spermatozoa or ova. Can we expect either spermatozoa or ova to survive and replicate in their natural environment without any support? Definitely not. In fact, many of the cell types isolated from an organism cannot be sustained even when we provide the best *in vitro* environment for them to grow in. Therefore, the argument that viruses should be excluded from the tree of life because they cannot sustain themselves under natural conditions does not hold. Also, 'nature' does not mean mere soil, light and water. It also includes all living entities, including plants and animals. Although viruses need host cells for survival and replication, we cannot argue that viruses will not survive in nature if we leave them alone, as hosts themselves are part of the continuum of nature. In fact, even animals and birds are not sustained in nature unless they obtain food from other sources of life, that is, plants or other animals. Thus, similarly to viruses, animals and birds are dependent on other species to be sustained in nature. So, virus replication in the host means that viruses replicate in nature. An interesting case is that of Sputnik, a recently described virus that exists inside another virus, acanthamoeba polyphaga mimivirus². If a virus

can live inside another virus, is the bigger virus similar to a host cell or is it simply a parasite within a parasite?

Pathogen recognition patterns, such as Toll-like receptors, are common features of all living organisms, including plants. In addition, Toll-related proteins of plants recognize viruses³. The fact that plants evolved millions of years before animals suggests that ever since the origin of life, living organisms have confronted viruses. We think that the argument about the polyphyletic features of viruses is not strong. Moreira and López-García agree that viruses evolve much faster than bacteria, archaea and eukaryotes. We argue that if organisms evolved equally fast, nature would contain a lot more species of life forms. Therefore, because the evolution of viruses is rapid in comparative terms it makes sense for viruses to be polyphyletic.

It is well known that all living organisms follow Darwin's theory of 'survival of the fittest': those organisms that cannot adapt to a particular condition become extinct. However, non-living objects do not follow this theory. If viruses are 'non-living' entities then they should not have the ability to adapt to a particular condition. However, most viruses, including human immunodeficiency and influenza viruses, undergo constant mutations, thereby changing their phenotypic characters to sustain themselves in their environment.

Evolution of viruses is most often driven by the host. Of particular interest is immune evasion by viruses, as best illustrated by the case of herpes viruses. These viruses are highly species-specific. Accordingly, there is often a phylogenetic distinction in the functions encoded by the herpesvirus genomes to evade immune responses. In some cases, a generalized function is observed but the gene products do not display homologues. For example, human cytomegalovirus US2, US3, US6 and US11 proteins affect major histocompatibility complex class I and class II synthesis, assembly and trafficking⁴, but no such homologues exist in murine cytomegalovirus even though the core (conserved) proteins are similar. However, it could still be argued that viruses adapted following speciation and that there would be no

evolution if there were no environmental pressure. But are we not taught in classical evolutionary biology that change or adaptation is due to the environment? And in the case of viruses, the environment is the body, its systems and its cells. Furthermore, most successful viruses either need to survive in the host for a long time by evading the immune system (for example, through latency or persistency) or need to change rapidly to keep up with the immune system.

Unlike the physical and chemical sciences, life science is not always fool-proof. The central dogma of replication (DNA to RNA to protein) is itself under scrutiny. Some RNA viruses, such as orthomyxoviruses, paramyxoviruses and picornaviruses, can directly replicate their RNA without being converted into DNA, whereas prions are proteins and lack nucleic acids but can replicate directly. Moreira and López-García¹ drew an analogy with a computer virus. However, this is stretching the argument too far, as computer viruses are not chemical or biological entities. And to include plasmids in the same league as viruses is also wrong. Plasmids neither actively enter cells, nor are composed of proteins. Life itself is derived from the assembly of non-living things: nucleic acids and proteins. How far do we go to define the tree of life — does it start only from the primordial cell or does it go further back?

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