What came first: the virus or the cell?

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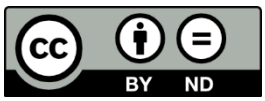


Abstract

A retrospective of the debates on the origin of life: the virus or the cell? The virus needs a cell for replication, instead the cell is higher on the evolutionary scale of life. Viruses appear to have played a role in events such as the origin of cell life and the evolution of mammals. Even the simplest bacteria is far too complex to have appeared spontaneously at the beginning of evolution. Subsequently, evolution has been able to produce increasingly complex systems. The first true cell may have already been a product of evolution, resulting from a primordial community.

What came first: the virus or the cell?

Viruses reproduce only inside the living cells of organisms, (Wu 2020) being known so far more than 6,000 species of viruses. (International Committee on Taxonomy of Viruses (ICTV) 2020) When it infects a cell, the viruses force it to rapidly produce thousands of identical copies of the original virus.

A relatively common misconception about what a biological virus actually is, is that a virus often refers only to protective capsules made up of proteins, which contain viral genomic information in the extracellular environment. (Jacob and Wollman 1961) This particle is a virion and is generally considered dead. Matti Jalasvuori (Jalasvuori 2012) highlights the difference between a virus and a virion, which allows us to appreciate viruses as evolutionary players or even as living organisms. (Forterre and Prangishvili 2009)

Virions are external, autonomous, consisting of genetic material (DNA or RNA molecules) that encode the structure of proteins, a protein layer (capsid), and sometimes an outer layer of lipids.

Viruses are far too small to be visualized with a regular microscope, with diameters between 20 and 300 nanometers. (Mahy 1998) The first images of them were obtained by electron microscopy in 1931 by German engineers Ernst Ruska and Max Knoll. (Fraengsmyr and Ekspong 1993) Rosalind Franklin discovered the complete structure of the virus in 1955. (Creager and Morgan 2008)

Viruses appear to have played a role in events such as the origin of cell life (Koonin, Senkevich, and Dolja 2006) and the evolution of mammals. (Gifford 2012)

The origin of viruses is unclear (they have existed since the first evolution of living cells. (Iyer et al. 2006) There are three main hypotheses that explain the origin of viruses: (Shors 2016)

1. The regressive hypothesis ('degeneration hypothesis', (Dimmock, Easton, and Leppard 2007) or 'reduction hypothesis': (Mahy and Regenmortel 2009) they come from small cells that previously parasitized larger cells.
2. The cell origin hypothesis ('wandering hypothesis') (Mahy 1998) or 'escape hypothesis': (B. W. J. Mahy and Regenmortel 2009) they come from bits of DNA or RNA that have 'escaped' from the genes of a larger organism. (Shors 2016)
3. The co-evolution hypothesis ('the first virus hypothesis'): (B. W. J. Mahy and Regenmortel 2009) they come from complex molecules of proteins and nucleic acid appearing simultaneously with the cells on which they would have been dependent.

One hypothesis claims that viruses have probably appeared several times in the past through one or more mechanisms. (B. W. J. Mahy and Regenmortel 2009)

Even the simplest bacteria is far too complex to have appeared spontaneously at the beginning of evolution. Subsequently, evolution has been able to produce increasingly complex systems. Matti Jalasvuori concludes that the first true cell must have already been a product of evolution, (Jalasvuori 2012) resulting from a primordial community. (Doolittle 2000) The community has evolved mainly horizontally by changing genetic information between protocells, rather than in a 'Darwinian' way, passing genes vertically to offspring. (Koonin and Martin 2005) It follows that the protocells themselves were not coherent genetic entities, but more or less random collections of independent genetic replicators, which evolved collectively thus maintaining the common genetic code. (Vetsigian, Woese, and Goldenfeld 2006) Since viruses or virus-like replicators are thought to be able to come up with new genes, then they could have been one of the elements in that primordial community.

Matti Jalasvuori states that viruses provide a possible explanation for the horizontal evolution of early life, as virions are essentially genetically encoded structures that mediate the cell-to-cell transfer of genetic information. As the primary system advanced, some of the first viruses established a permanent residence in some of the protocols. (Jalasvuori 2012)

Scott Podolsky (Podolsky 1996) described the different roles of viruses in theorizing the origin of life, from the 1920s to the 1960s. (Kostyrka 2016) He noted that viruses were integrated into life-origin scenarios characterized by a "nucleocentric approach", unlike a "cytoplasmic approach". The nucleocentric approach defined life based on self-duplication. (Podolsky 1996, 80) The cytoplasmic approach focused on the cytoplasm as a model to define life and understand its origin, conceived as self-regulation.

Podolsky identified three major roles of viruses in early life origin scenarios. (1) as a "metaphor" of life (conceptualized as an image of primitive life), as an "operational model" (provides, by analogy, a conceptual representation of possible mechanisms), and their phylogenetic role, conferring virus-centered nucleocentric arguments with a real "sense of historicity". (Podolsky 1996, 84) Thus, viruses could be seen as the "relatively unmodified descendants of the primordial precursor to all later life forms."

According to Gladys Kostyrka in *What roles for viruses in the origin of life scenarios?* (Kostyrka 2016) the conceptualization of viruses as inert products of living cells or extracellular agents had strong implications for the roles that viruses could play in life origin scenarios. The divergence between an "endogenous thought style" and an "exogenous thought style" has been particularly strong in the debates. Felix d'Herelle proposed a virocentric scenario of the origin of life. (Félix d' Hérelle 1926) For d'Herelle, viruses are not primitive life forms, (F. d'Hérelle 1928, 540) because they are parasites of cells. But viruses could represent relatively unchanged

descendants of primitive life forms (phylogenetic role), and could also serve as a metaphor for life (metaphorical role). (F. d'Hérelle 1928, 538) Based on a viral metaphor of life, d'Herelle hypothesized that the simplest forms of life are not cellular, but micellar.

The scenario proposed by Alexander and Brigdes in 1928 differs in many respects from d'Herelle's scenario. (Alexander and Bridges 1928) Their approach is nucleocentric, because they conceive of the virus as an example of life. They consider viruses as simple life forms ("ultrabionts"), but more complex than fundamental ones ("moleculobionts").

J. B. S. Haldane provided another example of the conception of life which, like d'Herelle, is not strictly nucleocentric, but nevertheless gives viruses important roles in the origins of life. But Haldane refused to call viruses "living" and rather described them as models for understanding the first "half-living molecules" (Haldane 1929) that might have existed before the formation of the first cell.

The phylogenetic roles of viruses have been particularly contested. Viruses would rather be the result of the reductive evolution of cells. (Laidlaw 2014) The Green-Laidlaw hypothesis or the retrograde hypothesis for the origin of viruses has convinced many biologists. (Podolsky 1996, 101–3)

The hypotheses of the origin of life due to viruses increased during the years 2000-2010. (Koonin and Dolja 2013) According to Gladys Kostyrka, the following syllogism would probably be accepted by many biologists: (Kostyrka 2016)

1. Viruses depend on cells (no virus could have existed before cells),
2. The search for the origin of life is to trace the appearance of the first cell,
3. Viruses are therefore excluded from discussions about the origins of life.

This syllogism seems to hinder the phylogenetic or historical role of viruses in the origins of life. However, Patrick Forterre hypothesized that viruses appeared before DNA cells and before LUCA (Last Universal Cellular Ancestor), (Forterre 2006) resulting in a phylogenetic role for viruses. According to Forterre, ancestral viruses did not contribute to the emergence of cell life; Cell life must have existed before, because viruses need cells to replicate. But viruses are said to have contributed to the origin of DNA cells. A simplified version of the scenario for the appearance of DNA is that RNA viruses appeared inside the second era of the RNA world, because RNA cells already existed and could be parasitized. (Kostyrka 2016) (Forterre 2005)

Confirmation of the phylogenetic role of viruses could therefore explain the problematic coexistence of two distinct ways of replicating DNA in the living world. This scenario also gives viruses an operational role. Viruses, for Forterre, have phylogenetic and operational roles, but they are not metaphors of primitive life. (Forterre 2016)

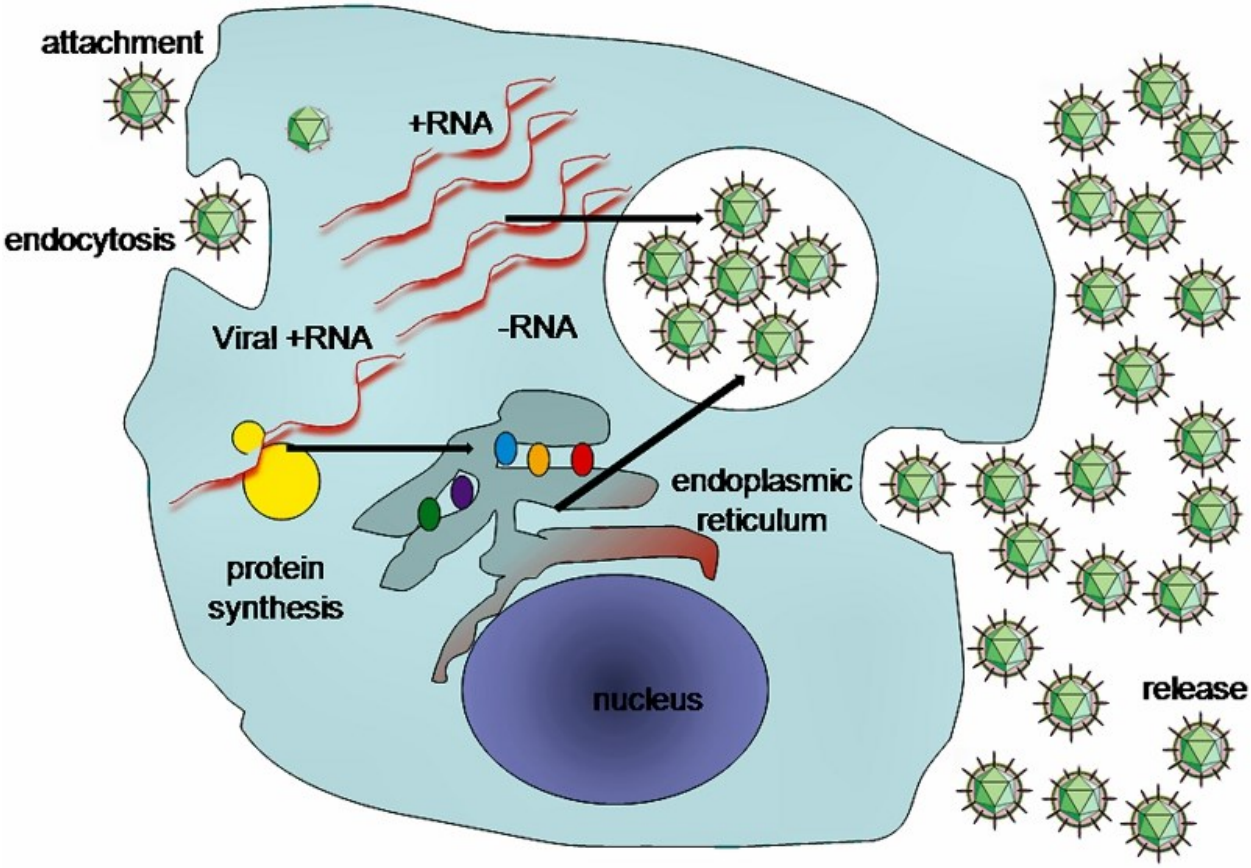
Eugene Koonin develops a virocentric scenario for the origin of life ("primordial virus world scenario" (Koonin 2009)). Koonin also assumes that viruses appeared during the second world of RNA, but rejects the alleged existence of RNA cells, mainly due to RNA instability. (Koonin, Senkevich, and Dolja 2006, 10) He argued that the first cells must have been DNA cells, so viruses must have appeared in a world without cells. Thus, Koonin rejects the common assumption that viruses cannot exist without cells. (Koonin and Dolja 2013, 550) In 2006, Koonin formulated the "ancient viral world hypothesis" that no gene is shared by all virus species - there is no common ancestor of all viruses, viruses have multiple origins. To explain the presence of these genes in existing viruses, Koonin assumes that they came from a primordial viral world and were conserved. (Koonin 2009, 60)

Koonin argues that the phylogenetic role of making it possible to switch from RNA to DNA is not just attributed to viruses. (Koonin and Dolja 2014, 289) He attributes a phylogenetic role to all components of viruses. To some extent, this hypothesis also provides a metaphor for life. (Koonin and Martin 2005)

The originality of Koonin's virocentric scenario is based on the underlying conception of viruses. Unlike Forterre, Koonin argues that viruses can exist and replicate without cells. Thus, Koonin also challenges the premise 1 of the syllogism. Moreover, the viral world "is by no means limited to the typical viruses that encode capsid". (Koonin and Dolja 2013)

Gladys Kostyrka concludes that Forterre and Koonin both argue for possible analogies between the real pathways of viral replication and those that may have existed in the early stages of life, and that viruses played an important phylogenetic role in the appearance of DNA and, more generally, in the evolution of replication mechanisms. But Forterre claims that viruses could only exist if there were cells, because viruses are intracellular parasites. Thus, the phylogenetic role of viruses would have taken place after the appearance of cell life. On the contrary, Koonin's conception of viruses contradicts the definition of viruses as intracellular parasites. For Koonin, viruses are fundamentally selfish genetic elements surrounded by a capsid. (Kostyrka 2016)

How could the virus play a role in the appearance of life if the existence of cells is a precondition for the existence of viruses? Gladys Kostyrka proposes several strategies. A first important strategy for introducing viruses into life-giving scenarios is to define life as acellular. A very different strategy for introducing viruses into life-origin scenarios is based on redefining cell life. (Kostyrka 2016)



A typical cycle of virus replication

There are six basic steps in virus replication: (Mahy 1998)

1. Attachment: binding between viral capsid proteins and specific receptors on the host cell surface. (Más and Melero 2013)
2. Penetration: virions enter the host cell through receptor-mediated endocytosis or membrane fusion. (Dimmock, Easton, and Leppard 2007)
3. Uncoating: removing the viral capsid. (Blaas 2016)
4. Replication: genome multiplication. (Isomura and Stinski 2013)
5. Assembly: a change in proteins (maturation) occurs after the virus has been released from the host cell. (Barman et al. 2001)

6. Release - by lysis, a process that usually kills the cell by breaking the membrane and the cell wall. (Dimmock, Easton, and Leppard 2007)

Viruses facilitate horizontal gene transfer, increasing genetic diversity. (Canchaya et al. 2003) There is an ongoing debate as to the extent to which viruses are a life form, or are "living organisms" (Rybicki 1990) and self-replicators. (Koonin and Starokadomskyy 2016)

Viruses undergo genetic changes through several mechanisms. In antigenic shift (when there is a major change in the virus genome) individual bases in DNA or RNA move to other bases - these changes can confer evolutionary benefits, such as resistance to antiviral drugs. (Sandbulte et al. 2011) When it may be the result of recombination or reassortment, influenza viruses can cause pandemics. (Hampson and Mackenzie 2006) RNA viruses often exist as quasispecies or swarms of viruses of the same species, but with slightly different nucleoside sequences of the genome. Such quasispecies are a major target for natural selection. (Metzner 2006) In genetic recombination a DNA is broken and then joined to the end of a different DNA molecule. Recombination usually occurs when viruses infect cells simultaneously. (Worobey and Holmes 1999)

Many organisms harbor a variety of genes unknown to science. (Mocali and Benedetti 2010) Many of these new genes are found in viral genomes. (Yin and Fischer 2008)

Viruses could be considered genetic modifiers. Viruses themselves do not evolve, but are evolved by cells. (Moreira and Lopez-Garcia 2009) But many viral genes do not appear to have cellular counterparts. (Yin and Fischer 2008) Viruses appear to have genes that produce structurally and functionally conserved proteins that have no apparent cellular ancestors. (Keller et al. 2009)

Viral infections usually cause an immune response that kills the virus. These immune responses can be triggered by specific vaccines. There are viruses, such as those that cause AIDS, and viral hepatitis, which manage to prevent these immune responses by causing chronic infections.

Some viruses do not cause apparent changes in the infected, asymptomatic cell (latency), (Sinclair 2008) a feature of herpes viruses. (Whitley and Roizman 2001) These latent viruses can sometimes be beneficial, increasing immunity against bacterial pathogens. (Barton et al. 2007) Other infections persist throughout life, (Bertoletti and Gehring 2007) so infected people are known as carriers because they serve as reservoirs of infectious viruses. (Rodrigues et al. 2001)

Virus transmission can be vertical (e.g., mother-to-child), or horizontal (person-to-person). Horizontal transmission is the most common mechanism of virus spread. (Antonovics et al. 2017) Epidemiology is used to break the chain of infection in populations during outbreaks of viral diseases, (Shors 2016) knowing the source of the outbreak and identifying the virus. Interruption can be done through vaccines, or isolation (quarantine), sanitation and disinfection. Vaccines can consist of attenuated viruses or viral proteins (antigens). (Palese 2006)

Matti Jalasvuori points out that, although viral infections can make the host resistant to subsequent infections by similar types of viruses, it is not a hereditary symbiosis. We are immune to chickenpox after an infection, but our children still have to infect themselves to become resistant. (Jalasvuori 2012)

During the spread of a virus epidemic, this integration of a virus into germ cells could provide an advantage to a person. (Jern and Coffin 2008) It is possible for the virus to establish a mutually beneficial relationship with its host. This symbiotic partnership would exist mainly at the level of genetic information, (Ryan 2009) but can still occur through a fusion of two distinct

entities of genetic reproduction. Although viruses could be considered to form symbiotic relationships through any mechanism, Matti Jalasvuori highlights some interesting aspects: How does this integrated virus affect the subsequent evolution of their hosts? The endogenous virus alters the genetic composition of chromosomes and can, for example, regulate the expression of host genes. (Jern and Coffin 2008) Some derived genes appear to have remained active for tens of millions of years. (Katzourakis and Gifford 2010) But even then, it is difficult to say with certainty how important these viruses were in the evolution of their hosts. (Jalasvuori 2012)

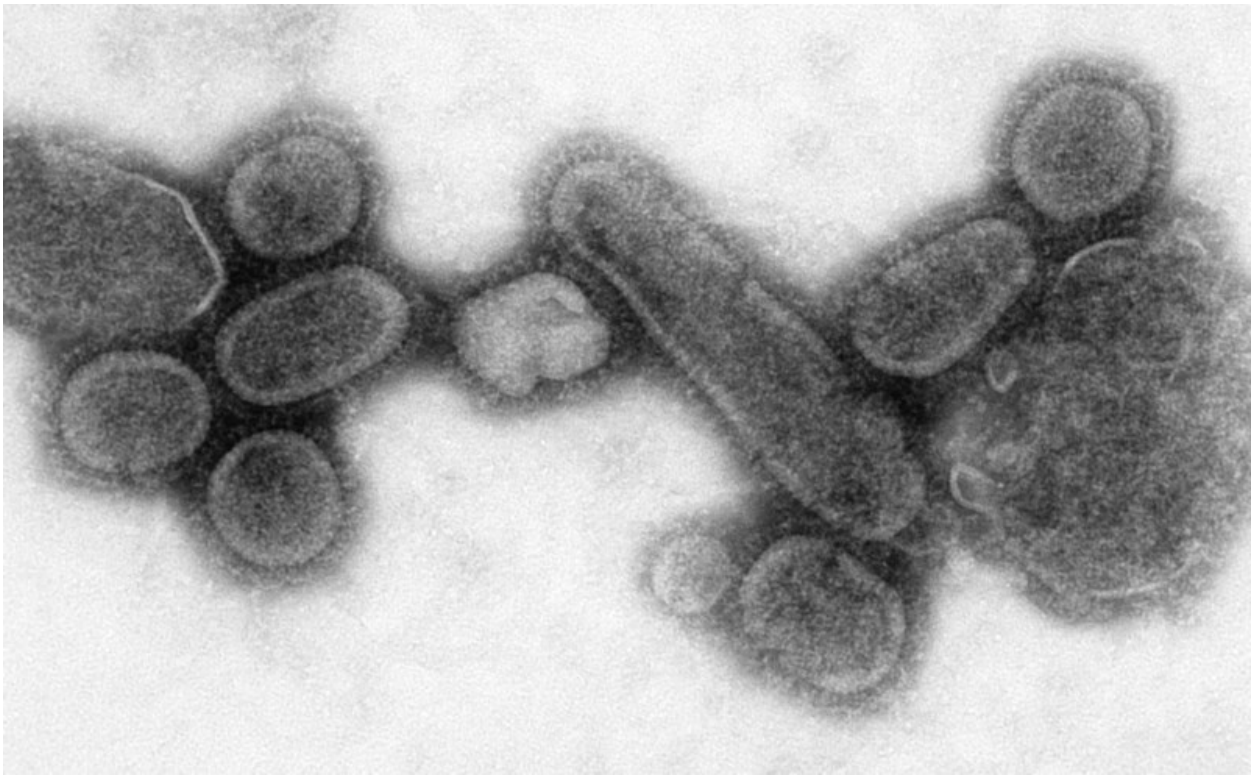


Image with electron microscope transmitting a recreated influenza virus from 1918

Viruses are an important natural means of gene transfer between different species, increasing genetic diversity and helping evolution, (Canchaya et al. 2003) being considered one of the largest reservoirs of unexplored genetic diversity on Earth. (Suttle 2007) They can also be used to manipulate and investigate cell functions, (Mahy 1998) being used as vectors to introduce genes

into the cells being studied. Virotherapy uses viruses as vectors to treat various diseases, including cancer treatment and gene therapy. (Jefferson, Cadet, and Hielscher 2015)

Many viruses can be synthesized "from scratch". The first synthetic virus was created in 2002. (Cello, Paul, and Wimmer 2002) This technology is used to investigate new vaccination strategies. (Coleman et al. 2008) It follows that viruses can no longer be considered extinct, as long as their genome sequence information is known and permissive cells are available.

The ability of viruses to cause epidemics has raised concerns about the possibility of their use in a biological warfare. The 1918 influenza virus was recently successfully recreated in a laboratory. (Zilinskas 2017) There are only two centers in the world authorized by the WHO to store smallpox virus stocks, which can be used as a weapon because the smallpox vaccine has sometimes had severe side effects, and is no longer commonly used in any country. (Artenstein and Grabenstein 2008)

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