VIRUSES:

THE SMALLEST INFECTIVE BIOLOGICAL ENTITIES

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What are viruses? How were they discovered? What do we know of their structure? How do they replicate and multiply? Where do they come from? Do we know of any viruses that are beneficial to us?

Today, the world faces an unprecedented threat from a virus. But this is not the first viral infection that we know of. Numerous diseases in plants and animals are caused by viruses. The common cold, dengue, smallpox, measles, rabies, polio, hepatitis, some kind of cancers, and AIDS are examples of the many viral diseases that have shaped human history.

Nature and structure

The existence and structure of viruses remained a mystery for a long time. Till the early 19th century, bacteria were believed to be the smallest disease-causing organisms (or pathogens). Simple experiments conducted by the German scientist Adolf Mayer on the mosaic disease in tobacco plants in 1883 played an important role in the discovery of viruses (see **Fig. 1**). Mayer showed that this disease could be transmitted by inoculating a healthy tobacco plant with the sap of an infected one. In 1892, Russian biologist Dmitri Ivanovsky passed the sap from infected tobacco plants through special porcelain filters. The pore size of these filters was small enough to prevent bacterial cells from passing through. Ivanovsky found that the sap remained infective even after all the bacteria from it had been filtered out. Around the same time, the Dutch microbiologist Martinus Beijerinck suggested that the filtrate in Ivanovsky's experiment had an infectious agent smaller than bacteria. He called

Fig. 1. Studies by multiple scientists on the tobacco mosaic disease played an important role in the discovery of the tobacco mosaic virus (TMV) as well as viruses in general. This infection causes a mosaic-like mottling and discolouration of leaves of tobacco plants.

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this infectious agent *"contagium vivum fluidum"*, meaning a contagious poisonous fluid. The American scientist Wendell Stanley crystallized the tobacco mosaic virus in 1935, demonstrating its particulate nature.

Stanley's achievement, for which he received the Nobel Prize in Chemistry in 1946, started an endless debate about the nature of viruses. At the heart of this debate is the question — should viruses be classified among living organisms or non-living matter? These tiny entities require a living cell, called a **host**, to multiply. Like living organisms, they have genetic material, the capacity to replicate and multiply, as well as cause disease in their animal, plant and bacterial hosts. Unlike living organisms, viruses do not respire, do not have their own metabolic machinery, do not grow, and can be crystallized. On the whole, they are among the most mysterious biological entities that we know of.

Viruses are so small that they cannot be seen with optical microscopes, let alone the naked eye. The largest known virus is only about 750 nm (1 nm = 10^{-6} mm or a millionth of a mm) in size. The structure of a virus is simple, and can be thought of as an 'infective particle with genetic material enclosed in a protein coat'. Its genetic material is in the form of one or two strands of DNA or RNA. This is used to identify and classify viruses. No known virus particle contains both kinds of nucleic acids. The protein coat, or **capsid**, of a virus provides structure and protection to its genome. Some viruses, like the ones causing the common cold, influenza, or COVID-19 in humans, have a phospholipid **envelope** over their protein coat. This envelope is derived from the host cell membrane, but can also contain virus proteins and glycoproteins. The protein capsid and the phospholipid envelope (if present) help the virus infect its host (see **Fig. 2**).

Replication and multiplication

Outside a host, viruses can be found in air, water, soil, and various surfaces as biologically inactive particles. On contact with a potential host cell, the virus starts behaving like a 'living' entity capable of replication and multiplication. This can be seen, for example, when the enveloped RNA viruses that cause the common cold in humans come in contact with any cell lining the human respiratory tract. A glycoprotein in the phospholipid envelope of the virus gets attached to a matching receptor on the host cell membrane. The virion (consisting of the outer capsid and the inner core of nucleic acid) enters the host cell through endocytosis, or fusion of the virus envelope with the host cell membrane. Enzymes from the host cell's cytoplasm dissolve the capsid, setting the virus RNA free. The virus RNA replicates and directs the synthesis of proteins for the virus capsid. In short, the virus genome takes control of the genetic and protein synthesis machinery of the host cell. Paralysed in terms of its own physiological and genetic functions, the host cell ceases to exist, releasing numerous newly assembled virus particles. Each of these virus particles can invade another cell or infect a new host (see **Fig. 3**). Often, a virion may enter its host, but remain in hiding. The virus genome establishes a relationship of co-existence with the host genome. The host develops disease symptoms, and releases virus particles only when this relationship breaks down (usually because of lowered immunity in the host). This is seen, for example, in *Herpes simplex* infections in humans.

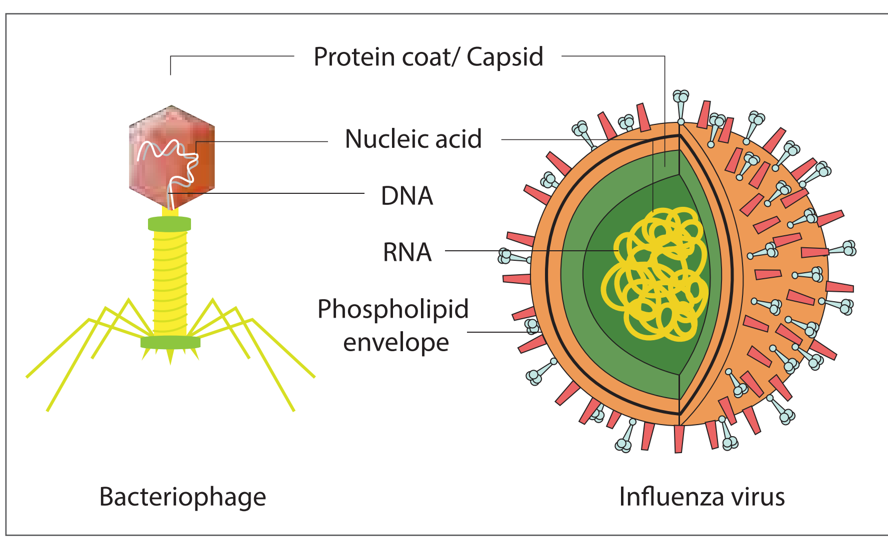

Fig. 2. The structure of a virus particle is simple. Its core consists of genetic material in the form of one or two strands of DNA or RNA. The bacteriophage (a virus that parasitizes bacteria) to the left has double-stranded DNA, while the influenza virus to the right has double-stranded RNA. This core is enclosed within a protein shell called the capsid. The capsid in some viruses, like the influenza virus, is covered by a phospholipid envelope.

Credits: Adapted from an image by Dr. Tim Sandle, Pharmaceutical Microbiology. URL: https://www.bbc.co.uk/staticarchive/2effc5b6f748963d346ae11763b12f9ef34ba8af.jpg.

Origin and evolution

Where do viruses come from? How have they evolved into the forms that we know of today? Scientists attempt to answer these questions in two ways. They look for genetic material, chemical signatures, or symptoms typical of virus infections in soil and fossils; and compare the genetic sequences of different viruses to estimate how closely they are related.

These studies offer some circumstantial evidence that the first viruses may have evolved around the same time as life evolved on earth. Although their categorization as living beings is debated, the genetic code of a virus, like that of all other organisms, is written in the universal language of nucleic acids. This suggests a close evolutionary relationship between viruses and the 'living' world. Interestingly, some studies suggest that the genomes of viruses infecting a host have more in common with the host genome than with viruses infecting a different host. Others show the presence of viral DNA sequences in the genetic code of their hosts. Such instances of 'genetic co-mingling' suggest that viruses have a long history. More recent studies reveal similarities between the genomes of viruses that infect two different host species, suggesting that a common ancestor of the two hosts may have been infected with a common ancestor of the virus. In addition, historical examples of parasitism, and the fact that all living organisms today are infected by at least one type of virus suggest that viruses may have been our 'evolutionary companions' through time.

But what is the nature of this relationship? Should one think of viruses as the most complex molecular compositions of nature, or as the simplest forms of life? While there is much debate among virologists, three main hypotheses have been articulated. According to the 'progressive' hypothesis, viruses may have originated as simple, naked, mobile fragments of cellular nucleic acid, which gained the capacity to enter and exit cells with damaged membranes. Through a progressive process, these fragments may have acquired the genetic sequences of a few structural proteins, and become capable of attaching to and infecting undamaged cells. In contrast, the 'regressive' hypothesis suggests that the viruses may have originated from more complex, free-living organisms. Through a regressive or reductive process, these organisms may have lost most of their genetic information over time and adopted a parasitic approach to replication instead. Both these theories are based on the assumption that viruses could not have existed as living entities before other living cells came into being. But what if the origin of viruses predates that of cells? According to the 'virus-first' hypothesis, viruses may have originated as self-replicating units in a pre-cellular world. Over time, these units may have evolved into the more organized and complex forms that we see today. Which of these is most plausible? At present, studies suggest the likelihood that viruses may have originated at multiple times, through multiple independent mechanisms. This is not all. Since viruses evolve quite rapidly, novel species (like SARS-CoV-2) are being discovered quite

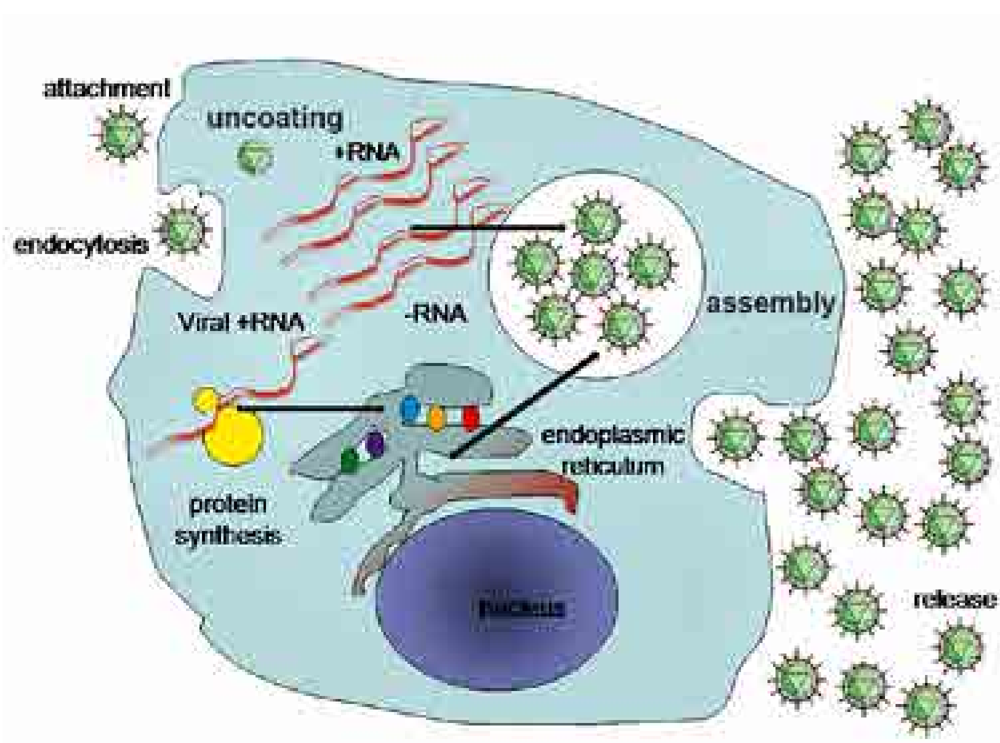

Fig. 3. A simplified diagram of the replication cycle of an enveloped RNA virus. Replication of this enveloped virus involves the (a) attachment of the envelope to the host cell membrane, (b) entry by endocytosis of the virion, (c) uncoating of the virus RNA by cellular enzymes, (d) virus RNA synthesis, (e) virus protein synthesis, (f) assembly of virus particles, and (g) release of virus particles with envelopes. Note that the genome of this virus is in the form of a minus strand of RNA (-RNA). This strand can act as a template for the synthesis of many complementary strands, called plus strands of RNA (+RNA). The +RNA is like an mRNA molecule, and can be immediately translated into proteins. It can also act as a template for the synthesis of more -RNA strands for the next generation of viruses.

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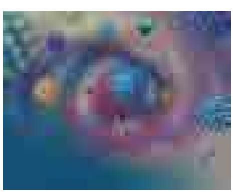
frequently. But tracing their origin, and understanding their evolution continues to remain both a challenge and a source of enduring curiosity.

Parting thoughts

Viruses are often seen only as disease causing microbes, but they interact with humans in many complex and diverse ways. Just as our body hosts bacteria that help in digestion, it also hosts many protective viruses. The bacteriophages (viruses that are parasitic on bacteria) found on the mucous membranes of our digestive, respiratory, and reproductive systems are excellent examples of this. Recent research shows that these bacteriophages protect us from pathogenic bacteria. Many of these phages are used in the treatment of dysentery, sepsis, skin infections, as well as infection by *Staphylococcus aureus* and *Salmonella sp.* Some viruses protect us from other pathogenic viruses. For example, the dormant form of *Herpes simplex* virus helps natural killer (NK) cells in identifying cancer cells, and cells infected with other viruses. Not only do viruses have an important role in microbiology and genetics, the treatment of viral and bacterial infections with bacteriophages is now an emerging field in medicine.

Key takeaways



- Viruses are the smallest biological entities, even smaller than bacteria. They cannot be visualized under an optical microscope.
- Viruses contain either DNA or RNA as their genetic material. No known virus contains both types of nucleic acids.
- The debate on whether viruses should be classified as living beings or non-living particles is ongoing.
- Once inside a host cell, the virus genome takes control of the genetic and protein synthesis machinery of the host cell to replicate and multiply.
- Outside a host, viruses can be found in air, water, soil, and various surfaces as biologically inactive particles.
- Current evidence indicates that the first viruses may have evolved around the same time as life evolved on earth, and that a close evolutionary relationship exists between viruses and the 'living' world.
- Three hypotheses — progressive, regressive, and virus-first — have been offered to explain the origin of viruses. Available evidence suggests that viruses may have evolved many times by many independent mechanisms.
- While viruses evolve quite rapidly and novel species are discovered frequently, tracing their origin, and understanding their evolution continues to remain a challenge.
- Viruses interact with us in complex and diverse ways. Some cause disease, while others protect us from diseases caused by pathogenic bacteria and other viruses.

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