

The Undefinable Links: Unraveling the Mysterious Relationships Between Viruses and the Human

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Abstract. The world of viruses is a captivating and complex field that consistently engages scientific inquiry and exploration. This article presents intriguing aspects of viruses, including their discovery, intricate structures, and taxonomic classification. It sheds light on the ongoing battle between humans and viruses, highlighting the remarkable progress made in combating and preventing viral diseases. Furthermore, it conducts a comprehensive examination to explore the dynamic interplay between viruses and humans, revealing their pivotal role in medicine and their potential as powerful tools for genetic engineering. This study not only reveals the significant implications of viruses in biomedical science and research but also provides an overview that promotes a broader understanding of their positive aspects in addition to the negative ones.

Keywords: Viruses, Human, Function.

1. Introduction

Nature never ceases to amaze us with its ability to upend our understanding of the world around us. Viruses, in particular, have proven to be a fascinating enigma, continually challenging our preconceived notions of what constitutes "life". But viruses are more than just scientific curiosities — they have played a significant role in shaping human life and evolution. From the common cold to deadly pandemics, viruses have been a constant presence throughout human history. And yet, despite their ubiquity, we are only just beginning to scratch the surface of our understanding of these microscopic entities. Therefore, to keep you up to date, the relationship between viruses and human life is the topic of this essay. In the first chapter, intriguing tidbits about these minuscule entities will be presented, including their discovery, structure, and classification. The second chapter will focus on the ongoing battle between humans and viruses and the incredible strides we've made in treating and preventing viral diseases. In the final chapter, I will delve into how viruses are turning from foes to friends, playing a role in medical treatments, and even serving as a tool for genetic engineering. As we unlock more of the secrets of viruses, we continue to rewrite our understanding of the natural world and our place in it.

2. A brief history of virology

The discovery of viruses and the evolution of our understanding of these infectious agents have been a saga spanning several centuries. In 1890, Koch postulated four criteria for establishing a causal link between microbes and diseases. This overturned the ancient doctrine of spontaneous generation and showed that bacteria can cause certain diseases. Koch's work laid the foundation for the discovery of viruses in 1892 by the Russian biologist Dmitri Iosifovich Ivanov sky. However, he observed that certain pathogens passed through filters that retained bacteria but could still infect other plants, although initially he thought it was a kind of bacterial toxin. It was not until 1898 that Beijerinck concluded that the tobacco mosaic virus was a "slimy liquid poison" that proliferated within living cells (Kammen, 1999). Based on our current understanding of viruses, they are obviously not liquid. But this discovery had to wait until the 1920s, when the invention of the electron microscope allowed scientists to directly observe viruses. Thomas Milton Rivers observed and defined viruses in 1926 as obligate parasites that required host cells to replicate instead of living organisms (History of Virology, 2023).

It was in the early 1950s that researchers were able to study a wider range of animal viruses to better understand their chemical nature and replication mode (Norrby, 2008). Advances in genetics and biochemistry, such as tissue culture techniques, led to Heinz Fraenkel-Conrat's 1955 *in vitro* disassembly and reconstruction experiments of the nucleic acid and protein subunits of the tobacco mosaic virus (TMV) and led to the Stalk vaccine and Sabin vaccine against polio. The subsequent decades saw the discovery of new types of viruses with a bunch of new technologies, and our understanding of viruses took off. One striking example is the treatment of HIV, where a cocktail of reverse transcriptase inhibitors in 1996 played a crucial role in resisting HIV infection.

3. Discovery of new viruses

Traditional virus discovery methods involved the inoculation of cell-free filtrates in suitable cell cultures, followed by the purification of the viruses and their characterization based on cytopathic effects, such as the formation of syncytia, lysis, and detachment (Datta, 2015). While the method is useful in characterizing molecules, establishing disease causation, and developing vaccines (Lipkin and Firth, 2013), it only applies to a limited set of viruses that can grow in culture systems.

The following PCR-sequencing and microarrays were comparatively faster and avoided the trouble of filtration and cultivation, as they led to the discovery of new variants of viruses. Nevertheless, these methods were critically dependent on prior sequence information of the virus family being investigated and were limited in their ability to amplify only a small portion of the viral genome (Datta, 2015).

NGS-based metagenomics enables the detection of the full spectrum of viruses, both known and unknown, within a sample. Virus enrichment methods, such as sequence-independent single-primer amplification, cDNA-AFLP, and rolling circle amplification, coupled with Next Generation Sequencing (NGS) platforms, have catalyzed the discovery of novel viruses, whose fruits include different parvoviruses, human herpesviruses 6 and 8, West Nile virus, etc. The rate at which novel virus sequences have been discovered has increased dramatically (Wang, 2015).

As we delve deeper into the microscopic world, our unspoken assumptions about these tiny entities are being overturned. Once believed to be a tiny, acellular pathogen that replicated solely within living cells, the old-school definition has expanded to include a wide variety of entities that do not fit neatly into this tidy classification. Take viroids for instance: these infectious single-stranded circular RNA pathogens lack the protein coat of a traditional virus and instead invade angiosperms through seeds or pollen, integrating into the nucleus for replication and causing disease (Diener, 1971). Similarly, the once finely accepted notion that viruses are the smallest of all species, dwarfed by even bacteria and fungi, was challenged with the discovery of the *Acanthamoeba polyphaga* mimivirus (Scola et al., 2003) and Pandora viruses (Philippe et al., 2013), the latter with their staggering 2,000 genes pushing the boundaries of what we thought was possible for these seemingly simple entities (Philippe et al., 2013), compared to a human with 20000 genes. And while it was once believed that viruses required a host cell to carry out their life cycle, exceptions like the Sputnik have proven this notion to be incomplete. This 50-nanometer marvel grows rapidly within the *Acanthamoeba polyphaga* mimivirus after a successful infection (Suzan-Monti et al., 2007). As we continue to uncover the mysteries of viruses, we must be prepared to update our understanding of these remarkable entities in the face of new discoveries, and classification is one way to do so.

4. Classification of viruses

The classification of viruses is a fundamental aspect of virology that helps us understand the differences between viruses, their characteristics, and the way we treat them. There are several methods of virus classification, with the most common being based on structure, genome, and pedigree.

The first method of classification is based on the structure of the virus, which is composed of a capsid and, in some cases, an envelope. The capsid is the outermost layer of a virus and is made up of protein subunits called capsomers. The two most common types of capsid structures found in vertebrate virus particles are helical and icosahedral (Crawford, 2011). Both structures are extremely stable and, in some circumstances, can be naturally formed even without the virus genome, as scientists discovered with the F1 protein of HPV, which has the ability to spontaneously self-assemble into icosahedral virus-like particles (VLP) (Bachmann et al., 1993). Some viruses that do not fit into either the helical or icosahedral categories are called complex viruses. They are rare in nature, but we see some archaic viruses with shapes such as bottle-shaped and droplet-shaped viruses.

The presence of an envelope surrounding the capsid is another factor in virus classification. Enveloped viruses are surrounded by a double layer of lipids, while viruses without envelopes are called naked viruses. The envelope influences the transmission of viruses (Flint et al., 2020), with studies suggesting that viruses transmitted by the faecal-oral mode of infection are rarely enclosed in a lipid envelope (Bushman et al., 2019), as the strong acid environment of the stomach impedes their survival.

The classification of viruses based on their genome and mode of information transfer is another essential aspect of virology. This method, known as the Baltimore classification, is based on their genome and mode of information transfer, in which viruses were combined and assembled into seven groups according to their genetic materials, number of strains, and sense of strain, with an additional category of retroviruses added later (Baltimore classification 2023). Such classification enables our understanding of the life cycle of viruses, thus enabling the development of targeted antiviral therapies. For example, viruses belonging to Group IV—ones with a positive-sense RNA genome—such as the coronavirus virus, rely on an enzyme called RNA dependent RNA polymerase (RdRp) to catalyze the replication of RNA from an RNA template. With such knowledge, RdRp inhibitors can be targeted in the design of drugs.

However, the mere seven categories provided by the Baltimore classification are insufficient to fully comprehend the genetic and biological characteristics of viruses. The third classification, which is based on viral pedigree, offers a more comprehensive approach to understanding viruses. The International Committee on Taxonomy of Viruses (ICTV) provides 15 levels of hierarchy to place each virus on its family tree. This nuanced classification allows us to understand the transmission and evolutionary relationships of viruses, monitor the emergence of genomes that are closely related to dangerous viral strains, and prevent global crises caused by viral outbreaks. Furthermore, this classification can provide evolutionary patterns that enable us to gain a better understanding of the origin and evolution of life itself.

5. Suspended civilization

Despite the cliché saying and universal truth that every coin has two sides, the name of virus comes before naming its benefit. Indeed, the impact of viruses on human civilization is a tragic tale, marked by widespread illness, death, and economic turmoil. From the bubonic plague to the Spanish flu and COVID-19, these microscopic organisms have left a trail of devastation in their wake. Among them, the smallpox virus stands out as one of the most notorious, responsible for killing millions of people and wiping out entire civilizations, including the Aztecs and Incas (Gunderman, 2019). Besides, the HIV virus has had a significant impact on public health and social attitudes toward sexuality and drug use since its discovery in the 1980s. In more recent times, the COVID-19 pandemic has brought the world to a standstill, infecting millions of people and causing widespread death and economic disruption. The pandemic has also exposed deep inequalities in our societies, with the most vulnerable populations suffering the most. So, it's no wonder humans continue to research and develop ways to prevent and treat those devastations. But fortune and misfortune are happening at the same time. The devastating battle against viruses in history has lectured humans on the idea of

coexistence and the principle of evolving to survive. But before everything else, let's see how viruses impact humans in a bad way, i.e., how do those tiny parasites cause disease in humans?

6. Pathogenesis

The pathogenesis of viral diseases can vary depending on the virus and the host it infects. It would be irresponsible to blame the virus solely; however, the mechanism of viral pathogenesis indeed plays a crucial role and can be attributed to three components: direct cell damage, interference with the immune system, and cell transformation.

First of all, some viruses can cause direct damage to cells, leading to changes in cell shape, permeability, or even cell lysis. For example, some viruses can induce the membrane to fuse between healthy cells and infected cells. Other viruses can burst cells after replication to a certain extent, leading to inside chemicals leaking and damaging surrounding cells. Second, viruses can also affect the immune system, either by activating it or suppressing it. Herpes simplex virus (HSV), which commonly causes orofacial and genital herpes, can occasionally cause severe complications, such as blindness, because it can trigger the production of various cytokines and chemokines, which are crucial for attracting leukocytes to the cornea (Smith et al., 2022). The final and also most concerning tactic employed by viruses is their ability to cause cell transformation, especially the transformation of tumors. In healthy cells, transcription factors such as P53 and Rb negatively regulate cell proliferation. However, viruses like the human papillomavirus (HPV), with its proteins coded by genes E6 and E7, can bind and inactivate the tumor suppressor proteins p53 and Rb, leading to uncontrolled cell growth and increasing the likelihood of cancer (Yim & Park, 2005). Viruses with cancerogenic ability are not prevalent, yet they are indeed terrifying.

7. Battle against viruses

Therefore, humans try to equip themselves with drugs and vaccines. Some work; others are on the way to work. On one point, all agree: their development exposes specific challenges. All I can mention is a general picture of what we are facing. To mention the strategies of antiviral drugs, for instance, the challenges are twofold. Traditionally, the targets of therapies against viruses were designed based on their life cycle; therefore, they basically fell into two groups: direct-acting antiviral drugs (DAA) and host-targeting antiviral drugs (HTA). For one group, DDA inhibits virus replication by targeting specific viral proteins involved in the virus life cycle, such as Sofosbuvir, Ledipasvir, and Daclatasvir, which have shown great promise in treating hepatitis C virus (HCV) by targeting viral proteins involved in RNA replication and protein processing (Abdelaty et al., 2020). However, the emergence of drug-resistant strains poses a significant challenge to the effectiveness of DAAs. For the other group, HTA has been proposed to be more effective in preventing viral infections as it is harder for viruses to develop resistance. However, HTAs can also be more toxic since they target host proteins. For example, in the case of HCV, antiviral drugs targeting the host membrane proteins CD81 and CLDN1 have shown potential for interfering with virus adsorption and cell-to-cell dissemination (Cann, 2006). On both sides, the side effects of these drugs on healthy cells and tissues must be carefully considered.

8. Human endogenous retroviruses

Although viruses are often associated with disease and suffering, the relationship between viruses and humans is much more complex and fascinating than we might realize. Human somatic cells contain 23 pairs of chromosomes with over 3 billion base pairs, and it's interesting to note that 8% of these are derived from ancient retro RNA viruses called human endogenous retroviruses (HERVs) (Lander et al., 2001). This might seem horrifying that viruses are capable of integrating their genes into the human genome; how does that happen? Why can't humans nip at the path of viruses? Do they cause harm to human beings? As a matter of fact, it was horrifying when I first heard of it, but I

no longer find it so. The virus with the capability to insert genes into human DNA is called a retrovirus, which falls into the sixth group of the Baltimore classification as single-stranded RNA viruses with a DNA intermediate in their life cycle. The reason why retroviruses do not stick to RNA in translation but retrotranscribe into DNA and then follow the central dogma is of interest to many virologists. While one acceptable reason to me for explaining their behavior is that the approach of inserting into the host genome can ensure their long-term survival. Think about it: if a virus infects germ cells, it can even be passed down through human generations. The reason we, as humans, do not forbid this pathway is also an interesting topic; if we think about this question in a simple way, those endogenous genes are our way of evolving as a natural way of being alive. Fortunately, most of the endogenous retrovirus's elements that have undergone numerous mutations, deletions, and rearrangements throughout their evolutionary history have become permanently silent, with a few functional genes still playing a critical role in promoting human existence by participating in the formation of the placenta, regulating host genes, and affecting immune responses.

The expression of human endogenous retrovirus type W in human placental tissue is a fascinating example of how HERVs impact human evolution. Syncytin-1 and Syncytin-2, the envelope proteins originally encoded by HERV-W, functioned as viral fusion proteins that facilitated cytoplasmic diffusion (Mi et al., 2000; Carriappa et al., 2003). However, after the retrovirus integrated into the human genome and was expressed, the villous cytotrophoblasts in contact with the mother's blood fused to form the syncytiotrophoblast, the placental barrier between maternal and fetal blood. The presence of this structure eliminates the gap between the placenta and the mother, preventing the mother's white blood cells from entering and avoiding an immune response against the embryo (Syncytin-1, 2023). HERVs have also been found to play a direct role in shaping cell type- and species-specific chromatin architecture, as HERV-H elements contribute to the formation of TAD boundaries, which are three-dimensional structures of chromatin (Zhang et al., 2019). Furthermore, HERVs have also been found to have a significant impact on the evolution and function of the human natural immune system (Grandi & Tramontano, 2018). They are believed to modulate the innate immune system, leading to inflammatory and autoimmune disorders, but they also have immunosuppressive properties that can control excessive immune activation.

9. From foes to friends

The complex and dynamic relationship between viruses and their hosts is exemplified by HERVs. Contrary to traditional views, viruses are not just harmful; they have played significant roles in the evolution and function of human genomes. With humans gaining more knowledge in this field of virology and advancements in engineering allowing us to manipulate viral genomes and harness their unique properties, we are actively turning these seemingly hostile organisms into friends. A flourish in medical treatments using viruses as vectors can illustrate the point. But not only in medical treatment; in other aspects of human life, the magic of the virosphere unlocks new possibilities for understanding humans ourselves.

First and foremost, comes gene therapy. Viral vectors have become essential tools in the field of genomic medicine, with an estimated 70% of clinical practices for nearly 3,000 gene therapies using viruses as vectors (Beitelshes M., Hill A., Rostami P., Jones CH., and Pfeifer BA.) This portion can contribute to the natural characteristics of viruses, such as being recognized by cell receptors, continuously replicating during their infection cycles, and, for some, inserting foreign genes into the host genome. While gene therapy involves artificial methods to implant useful target genes in organisms, viral vectors are a scientist's dream come true. For example, adenovirus, adeno-associated virus, herpes simplex virus, retrovirus, and lentivirus are some of the most commonly used viral vectors and have been used in treating a bunch of diseases (Lundstrom, 2018). Some viruses, such as oncolytic viruses like the herpes simplex virus (HSV), not only act as delivery vectors for gene therapy but can also selectively infect and destroy tumor cells while simultaneously stimulating immune responses (Niemann & Kühnel, 2017). When HSV is used for oncolytic therapy, knocking

out the main gene that HSV infects and replicates in normal cells can improve the targeting of HSV-infected tumor cells and enable them to selectively replicate in tumor cells (Tang et al., 2022). Besides, viral vectors are also being used in the development of vaccines. In agriculture, viral insecticides, such as baculoviruses, have gained popularity due to their effectiveness and safety (Haase et al., 2015). Phage therapy has emerged as a potential alternative to antibiotics for treating bacterial infections (Lin et al., 2017). All in all, viruses, under the common perception as harmful agents, have opened up new avenues of research and treatment. With their innate ability to penetrate host cells, they have provided scientists with a powerful tool to unlock the mysteries of disease and cure what was once incurable.

10. Conclusion

The world of viruses is a fascinating and complex topic that continues to be studied and discovered. As novel means are introduced to discover more and more viruses, new classifications are introduced to unroll the panorama of virus species. While viruses can have devastating effects on society and cause significant harm to humans, they also play an essential role in regulating the human genome and shaping human evolution. Despite the ongoing challenge of developing effective therapies against viruses, the use of viruses as vectors in genetic medicine and other fields offers promising possibilities for the future. Viruses are magical beings that always challenge our conception; with each new discovery, we move closer to unlocking the mysteries of the virus and the incredible potential it holds.

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