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Future Therapy

Virophages – Future Therapeutic Hope for Viral Diseases

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ABSTRACT

Virophages are viruses parasitizing another virus for their survival. These are circular, double-stranded DNA viruses which have a wide range of habitats including human and animal gut, soil, air, bioreactors, sludge and aquatic environment. Till now, six virophages have been isolated and identified. Besides only four conserved genes, their genomes display a wide variability. They also help as biodiversity agent and nutrient cyclers in aquatic regimes. Virophages also induce evolutionary course of the virus they infect. Scientists have started working on the concept of removal of virus population with the help of virophages just as Bacteriophages do with bacteria. The present article explores the virophages in brief and discusses their potential role in future therapeutics for treatment of viral diseases.

KEYWORDS: Sputnik, Acanthamoeba Polyphagia, Mamavirus

INTRODUCTION

Viruses are one of the most enigmatic entities on this planet. After Beijerinck coined the term "*contagium vivum fluidum*" (Latin for "contagious living liquid") for these pathogens, the living status of viruses is still disputed among scientists. These particles can control the host cellular machinery for their reproduction and can affect the life cycle of the host (Saenz & Roder, 2010). Ability of reproduction is one of the most fundamental features related to life, but due to rest of the characteristics these are still kept between the living and non-living entities.[1,2]

Virophages (virus infecting virus) has totally turned the thought wave about viruses in a newer direction. These are group of small viruses with double stranded DNA and can co-infect eukaryotic cells.[3]The discovery of Virophages as Giant viruses (Mamavirus) by La Scola and associates in 2008[4]is important evidence proving them as living entities. Since then, six virophages have been isolated from various environments.

DISCOVERY OF THE FIRST VIROPHAGE- *SPUTNIK*

La Scola and associates described *Acanthamoeba polyphagia* Mimivirus (APMV) as the first member of the Mimiviridae family in 2003. Mimivirus; meaning a microbe mimicking virus was initially isolated in 1992 from the water of a cooling tower during a pneumonia outbreak in Bradford, England and initially thought to be a type of small gram-positive *cocci* and named as "*Bradford coccus*" having atypical characteristics of viruses. But the true nature of the organism was revealed through electron microscopy as non-enveloped, icosahedral particles of 500 nm diameter.[5]and presence of a typical viral eclipse phase and further genome sequencing confirmed that mimivirus ("microbe mimicking") was indeed a virus co-habiting in a cytoplasm of *A. polyphagia*, a free living amoeba. This discovery revived the debate of viruses as living microorganisms.[6]

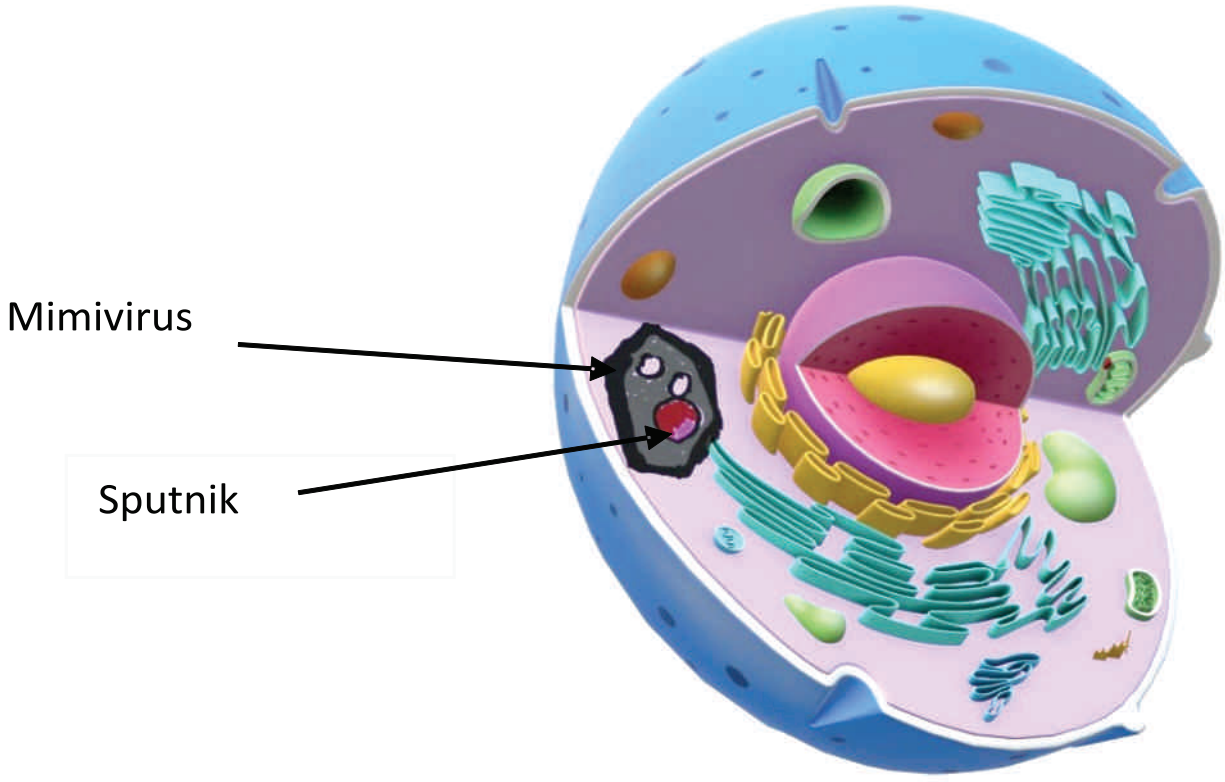

Figure 1: Diagrammatic Representation of *Sputnik* Virophage

Later on, a new giant virus called Mamavirus was discovered in the water of a cooling tower in Les Halles, France[4] which resembled Mimivirus in many aspects. Interestingly, a small satellite virus was found associated with mamavirus and named as Sputnik- (a Russian word meaning satellite) which was replicating within mimivirus, using mimivirus resources and further impairing mimivirus replication leading to generation of defective mimivirus particles.[4,7] This was affecting ability of mimivirus to destroy *Acanthamoeba* which was reduced by 13 percent.[7] *Sputnik*as a true "parasite" of mimivirus was then proposed to be the first virophage(in analogy to bacteriophages).[4] Giant viruses and virophages tend to infect a variety of protists and play important roles in regulating the population dynamics between protists and their viruses.[8,9]

VIROPHAGES TILL 2021

With recent advancements in molecular techniques, six virophages namely, *Sputnik, Sputnik2, Sputnik3, Zamilon, Zamilon2* and *Mavvirus* as well as one virophage like element (PgVV6) have been isolated and sequenced till 2021.[3] *Sputnik2, Sputnik3, Zamilon, Zamilon2* and *Mavvirus* are non-enveloped viruses, having small icosahedral capsids (diameter of 35–74 nm), with genomes ranging from 17 to 19 kb in length.[10]

Virophages have a distinct abundance and cosmopolitan distribution, involving almost all geographical zones and a variety of unique environments ranging. Their genome sequences have been detected from the deep oceans to land environments, plant rhizosphere, soil, air, glaciers, as well as from human & animal gut.[11,3] There is still very limited evidence of infection of human beings with Giantviruses, though; these have been isolated from human lung and fecal samples.[10] These clearly suggest existence of virophages on Earth and future researchers may bring notice towards presence of more such organisms.

Virophages, like other viruses, are often thought in a negative manner, as a damaging agent to the human health. In fact their philosophy is different. Observational studies have pointed that all virophages isolated so far have a common mission. And that is 'Not to harm the host but harm the virus (Helper virus) infecting the host'. Based on this concept the Virophages could be used to treat complex viral infections such as HIV, Zika and presently prevailing pandemic of SARS-CoV-2. This is not a farfetched dream but in fact a reality that people have started thinking in this direction.

FUTURE THERAPEUTICS

Study on *Sputnik* have shown that it spreads by hijacking the replication machinery of the giant virus named Mamavirus.[12] Subsequent studies further suggests that Virophage invades the viral factories of helper virus in which they live. They knock down the helper virus genes, by deleting fragments of its RNA. Besides this Virophages also utilizes proteins in cellular interaction to inhibit the helper virus.[13] Considering all these mechanisms a synthetically engineered Virophage – based

treatment can be developed against many viral diseases which at present have no definite effective therapy. If the proposition is valid; Virophage proves to be an effective and elegant agent against the viruses.

Let us take an example of SARS-CoV-2. If it is possible to develop a Virophage that is quite identical to SARS-Cov-2 in most respects but genes for RNA polymerase can be knocked down and instead add a gene for Reverse Transcriptase (RTase).[14] With this altered genetic pattern, when the Replicase- Transcriptase complex is formed, it will contain RTase but lacks Replicase. The absence of Replicase (RNA – dependent RNA polymerase) makes the Virophage to compete for it with the helper virus (In this example the Coronavirus). Moreover, the replication and expression of Virophage genome will produce Reverse Transcriptase and lead to Reverse Transcriptase of RNA of Viral and Virophage. This Reverse Transcription will prevent the further replication or translation of viral RNA. This genetically engineered Virophage will inactivate the helper virus (In this example the Coronavirus) and will not allow to cause any cellular damage.[15]

A very interesting phenomenon has also been observed that can be utilized as a prophylaxis for viral diseases. Evidence shows that there are some Virophages that infect the host cells without helper Virus and remain dormant. When the cell get infected by the helper virus, these virophages start activating and impose their inhibitory action against the virus.[16] This is really a very promising field in to utilize Virophage as treatment, as prophylaxis and may have potential to develop vaccine on this concept.

CONCLUSION

At the present moment, the study of Virophages is still in infancy and more in depth research is required to understand properly their full potential. It is hoped that in future the strategy for employing viruses (Virophages) against viruses will soon be utilized for betterment of Humanity suffering from devastating viral diseases.

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