Satellite Viruses: A Literature Review

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Abstract:

Viruses as a whole have long been an infectious and deadly force of nature that has caused countless deaths and disfigurements, not only in humans but in plants and animals. Countless diseases throughout history can trace their origins back to viral infections and thus, created the necessary field of virology. With that came the discovery of satellite viruses, a subfamily of smaller viruses, with genomes of 0.22-1.5kbp, that utilize “helper viruses” to perform necessary actions required for the satellite’s survival. Whether the interaction between a satellite virus and its helper virus is symbiotic or detrimental to the helper is dependent upon the species of the satellite. The existence of satellite viruses is a recent discovery which limits the available facts regarding them, but new information is being uncovered every day and the study of satellite viruses is an expanding and promising field. Satellite virus genomes vary, with discoveries including single-stranded RNA, single-stranded DNA, and double-stranded DNA satellite viruses.

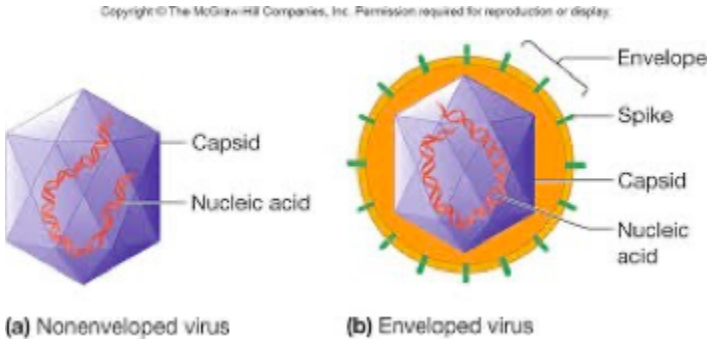
The Viral World

From chickenpox and influenza to human immunodeficiency virus and coronavirus, viral diseases have long been inconvenient and deadly infections that have caused countless deaths throughout human history and have thus, been an area of study for hundreds of years. Tobacco mosaic virus(TMV) was the first non-bacterial pathogen to be synthesized from a diseased organism, tobacco plants, and opened the door to an entirely new viewpoint of disease and medicine[1]. After this discovery was published in an 1892 paper, countless new and innovative experiments were conducted utilizing TMV as an ideal viral subject[1,2]. In the 1930s, research into the growth and replication of viruses had begun with the growth of the herpes simplex virus and vaccinia virus could be grown on a chorioallantoic membrane of an embryonated chicken egg[3]. By the 1960s, there was a much better understanding of viruses and the field of virology had taken off. As the development of artificial medium utilizing cell culturing of explant cultures, organ cultures, and monolayered cultures became predominantly used, the study of viruses expanded[3].

The virus reproductive cycle begins with viral entry, which is mediated by receptors on the host cell membranes[4] and is followed by genome replication and translation. Genome replication requires the formation of replication complexes that allow the genome to replicate either in the nucleus or cytoplasm utilizing DNA or RNA polymerases. The virus is then released from the cell or lyses the cell to allow the virus to be enveloped by the cell's membrane to increase its survival in the host[5]. Variations of this general mechanism of utilizing the host's cellular machinery to create new viral particles is the backbone of most viral replication and holds the potential to cause massive damage to vast areas of tissue following mass lysis of infected cells.

Prior to the discovery of satellite viruses, it was believed that the genome of every virus encodes one or more capsid proteins. Multiple copies of the capsid protein(s) assemble into organized structures known as capsids that are usually icosahedral or helical in shape. The primary function of the capsid is to surround and protect the viral nucleic acid. Many viral capsids are surrounded by an envelope (a host-derived lipid membrane in which viral structural proteins are embedded). These viruses are known as an enveloped virus (**Figure 1**). If there is no host-derived lipid membrane, the virus is referred to as a non-enveloped (or naked) virus. Virus genomes exist in multiple forms and can be DNA or RNA or double-stranded or single-stranded (**Figure 2**).

Figure 1. Viral structure

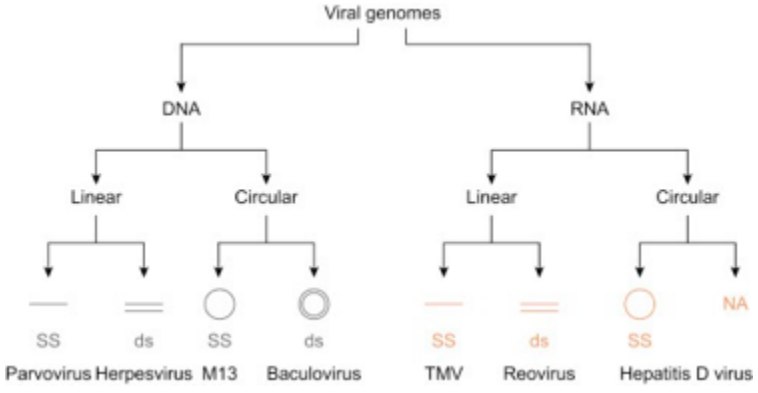


Satellite Viruses

Though regular viruses such as influenza virus are the most widely known and commonly addressed form of viral infection, additional levels of complexity exist within the viral world at a subviral level. Smaller disease causing agents such as defective interfering viruses, satellite viruses, and viroids also exist as components of viral infections[6]. Defective interfering viruses are mutated viral strains that have lost or altered some aspect of their genome that prevents them from successfully replicating without simultaneous infection from another virus, normally the parent virus[6]. Viroids are “naked” viruses that exist solely as circular RNA molecules that infect plants without encoding any proteins[6]. Satellite viruses can be thought of as a mixture of these defective interfering viruses and viroids. Just as defective interfering viruses are unable to replicate and infect cells without the coinfection of another virus, satellite viruses also need helper viruses to remain pertinent. Similarly to viroids, satellite viruses are very small, with genomes ranging from 0.07-11kbp[6]. Additionally, similar to viroids, a majority of the satellite viruses that have been identified have been shown to infect plant based viruses[7].

The main delineation between satellite viruses and other viruses is that satellite viruses do not encode their own capsid proteins, but instead, scavenge them from other viruses (known as helper viruses). To be classified as a satellite virus: 1) The virus must be dependent upon a helper virus to replicate, 2) the helper virus must not be dependant on the satellite virus for replication, and 3) there must be no significant homology between the genomes of the satellite and helper viruses[8]. Just as viruses require cellular machinery to reproduce and survive, some smaller viral entities termed “satellite viruses” also require other “helper viruses” to survive.

Figure 2. Viral Genomes



Current Satellite Viruses

Following the segregation and identification of the TMV and the many years of additional study and research that led to the very study of virology, the first satellite virus to be identified was the satellite tobacco mosaic virus(STMV; genus *Virtovirus*) in 1962[9]. Since this initial discovery, satellite viruses have been identified in association with multiple different helper viruses and in a plethora of different hosts. Select satellite viruses are summarized in Table 1. Maize white line mosaic satellite virus was discovered in association with Aumaivirus, panicum mosaic satellite virus with Papanivirus, Tobacco necrosis satellite virus with Albetovirus, Macrobrachium satellite virus 1, and Nilaparvata lugens commensal X virus are recently discovered single stranded RNA satellite viruses associated with plant diseases[10,11,12,13,14]. One unique discovery in satellite viruses is the Chronic bee-paralysis satellite virus, which is a satellite virus associated with a virus that induces paralysis in honey bees[15]. These viruses are small and incapable of replication without coinfection of cells with other viruses. Additional satellite viruses that contain unique and potentially useful mechanisms are those of the Lavidaviridae family[16]. These viruses are considered virophages, as they are essentially viralytic parasites that invade and induce a disease state in mainly giant viruses. Some satellite viruses in this family are the Sputnik, Zamilon, Mavirus, and lake virophages found in Yellowstone National Park and China[17,18,19,20,21,22,23,24]. These examples show the extent and diverse applications of satellite viruses on the viral domain as a whole. Some satellites are beneficial and aid in infection of hosts while others have proven detrimental to their helper viruses and cause natural selection in the viral world.

Table 1. Satellite Virus Overview

Satellite	Family	Helper	Host	Genome
STMV	Unassigned	TMV	*Nicotiana glauca*	ssRNA
SPMV	Unassigned	panicum mosaic virus	Millet and switchgrass	ssRNA
STNV	Unassigned	TNV	Tobacco plants, french beans	ssRNA
SV-MWLMV	Unassigned	MWLMV	Grassy weeds, sweet corn, maize	ssRNA
XSV	Sarthroviridae	Macrobrachium rosenbergii nodavirus	Giant freshwater prawns	ssRNA
NLCXV	Sarthroviridae	unassigned	*Nilaparvata Lugens*	ssRNA
CPVA	Sarthroviridae	CBPV	*Apis mellifera L.*	ssRNA

Sputnik Virophage	Lavidaviridae	Mimivirus	amoeba	dsDNA
Zamilon Virophage	Lavidaviridae	Mimivirus	amoeba	dsDNA
Mavirus Virophage	Lavidaviridae	*Cafeteria roenbergensis* virus	protists	dsDNA
Organic Lake Virophages	Lavidaviridae	variety	Variety of protists	dsDNA

The First Identified Satellite Virus

With TMV being considered the ideal model for viral research for such a long time, it is only fitting that the most well documented satellite virus to date would be the satellite associated with it, Tobacco Mosaic Satellite Virus(STMV). This satellite virus is found in the *Nicotiana glauca* plant and is unique among other satellite viruses due to its host virus being a rod shaped virus[25]. STMV is found alongside tobacco mild green mosaic tobamovirus, or TMV-U2 and has been shown to only replicate in tobacco leaves following prior infection of TMV-U2[25]. STMV's dependance on TMV-U2 for replication has been additionally verified through protoplast inoculation experiments[26]. On a microscopic scale, STMV induces vesiculated membrane bound accumulations of viral crystals and protein bodies within infected cells that are believed to be sites of replication[27]. In dual inoculated studies, these replication sites in STMV infected cells seem to be compartmentalized separately from the replication cycle of TMV-U2[27,28]. STMV is an icosahedral virus made up of 60 of the same capsid protein subunits enveloping its genome[29]. The STMV genome consists of 1059 nucleotides with 5' UTR stem loops and 3' UTR pseudoknots, making up areas of strong RNA interactions resulting in double stranded RNA regions[33,34]. While these genomic structures provide a measure of reliability to the structure and action of the satellite virus, it has been deduced that variations between strains can account for STMV infections alongside different TMV strains due to alterations at the 5' and mostly 3' end of the genomes[35,36]. Additionally, the encapsulation of the genome is not consistent throughout all variations of the strain of satellite virus[25].

Though the satellite virus can replicate within the tobacco leaves, it does not show significant changes in visible symptoms when compared to those transfected with TMV-U2 alone[25]. TMV-U2 is also found in other agricultural pepper, tobacco, and tomato plants. A dual infection of STMV and TMV-U2 shows little compounding action in symptoms compared to TMV-U2 infection alone[34]. However, dual infection occurring in jalapeno and pimento peppers, additional hosts for TMV-U2, shows significant changes in symptoms manifesting as severe blistering and yellow discoloration of the leaves[34]. From the differential symptoms in different host organisms, to its variability allowing symbiotic relationships alongside different helper cell variants, the unique properties of STMV encapsulate the broad and widely unknown nature of these newly studied viruses.

Panicum Mosaic Satellite Virus

While STMV is the most thoroughly studied satellite virus, many studies have been conducted on the panicum mosaic satellite virus (SPMV). SPMV is a satellite virus that co-infects millet and switchgrass alongside its helper virus, panicum mosaic virus (PMV)[35]. SPMV contains an 826 nucleotide genome formed into a 16 nanometer icosahedral particle[10]. Dual infection of SPMV and PMV have shown to increase the symptoms of infection significantly. The method by which this is believed to occur is by the satellite virus cataysing and upregulation of the replication of PMV, causing a more robust infection and response in the host organism[10]. Alone, PMV often induced slight stunting and small chlorotic mottles in millet plants, but with PMV + SPMV infection, a millet plant shows significant stunting of growth, inability to produce fertile seeds, and extremely vibrant chlorotic banding that has even been observed to progress to bleaching and necrosis[10]. Experiments in pearl millet plants showed a two to three fold increase in PMV RNA when associated with SPMV when compared to single inoculations, similar host rRNA decreases in the infected leaves regardless of dual or single inoculation, and the presence of PMV and SPMV RNAs in the sucrose density gradients in distant, uninoculated leaves[10]. These results aid in the conclusion that the co-infection of PMV and SPMV exacerbates the viral infection by increasing the spread of the viral complex through uninoculated leaves, increasing the titer of virus, and increasing the visible symptoms[10]. The method by which this is done may be increasing the viral concentration in each cell or infecting a larger number of cells to allow easier movement of the virus throughout the organism[10].

Tobacco Necrosis Satellite Virus

Tobacco necrosis satellite virus (STNV), is associated with strains of the tobacco necrosis virus (TNV). This virus can be grouped into one of two serotypes, A and D, that interact entirely differently with one another and with STNV[36]. These serotypes then can be reduced into more specific strains AA, AB, and AC making up Dutch cucumber necrosis virus, AF and AS making up bean stippled-streak virus, and DD and DE[12]. Studies presenting dual and singularly infected leaves with variably mixing TNV and STNV strains with antiserum to STNV were done to identify which stains perpetuated the replication of STNV. This study resulted in the finding that all strains interacted with STNV to allow replication to some extent except strain DD[12,36,37]. Strains AA, AB, and AC significantly increased STNV number, while DE only slightly increased STNV number[12]. Additionally, data shows that while the strains induce replication of the STNV, TNV experiences a resulting decrease in lesion-size and concentration[12,36]. Though these strains are closely related, their interactions with STNV are varied and dependent upon the strain. Also, STNV can be divided into multiple strains, SV1, SV2, and SV3. Conversely to the previously discussed study, another was done to identify any alterations in replication and TNV interaction based on the strains of STNV. This study found similar results, stating that strain D did not induce replication in any of the strains of STNV[36]. Further, the deduction was made that the correlation between strain interaction of TNV and STNV is more correlated with the host that the viruses infect, meaning that the serological commonalities are less important than the host preferences of the strains[36]. With strains that replicate more effectively in tobacco and those that replicate more efficiently in French beans interacting with one another, the instances of overlap between the satellites and their helpers are increased[36]. The synergism between tobacco

necrosis virus and tobacco necrosis satellite virus is a very complex example of how interactions between satellite viruses and their helper cells are dependent upon a multitude of factors.

Maize White Line Mosaic Satellite Virus

Maize white line mosaic satellite virus (SV-MWLMV), utilizes Maize white line mosaic virus, or MWLMV, as its helper virus to infect grassy weeds, sweet corn, and maize[38]. MWLMV causes immensely stunted growth and a specific chlorotic banding of white lines that cause an overall 44% yield loss and 21% height reduction of infected plants[39]. SV-MWLMV was first classified as a satellite virus following a 1990 paper performing cDNA cloning and a hybridization analysis showing that MWLMV could affect maize alone, while SV-MWLMV could only infect alongside MWLMV and no homologous genomic regions between SV-MWLMV and MWLMV[38]. Sequence analysis of SV-MWLMV showed a 4293 nucleotide RNA genome that contains five open reading frames creating a 17 nanometer diameter[38,39]. Unique to other plant infecting satellite viruses like SV-TMV, SV-PMV, and SV-TNV, there was no -AGGA- translation initiation signal upstream of the initial AUG start codon, suggesting a possible divergence of ancestry between these four satellite viruses[38].

Satellite Macrobrachium rosenbergii nodavirus

A 2003 study addresses the existence of an “extra small virus”, or XSV, that is associated with Macrobrachium rosenbergii nodavirus(MrNV)[40]. This nodavirus has been shown to induce white tail disease in giant freshwater prawns[41]. This disease induces a clinically relevant white tail, vast muscular necrosis causing smaller yields, and often, death[41]. This disease is only present in prawns containing both the MrNV and XSV[41]. Diseased prawns contain two disease particles, the large 27nm diameter icosahedral named MrNV and the smaller 15nm diameter icosahedral XSV proposed satellite virus[42,44]. Both of these particles contain a genome made of single stranded RNA with XSV not containing genes encoding its own RNA polymerase[42,43]. Additional genomic sequencing shows that XSV contains 796 nucleotides that encode a capsid protein, CP-17, making its genome significantly different from its proposed helper MrNV. With these deductions, XSV is shown to have many of the satellite virus features and may therefore be the first identified satellite virus corresponding with a nodavirus[43]. However, this small virus does encode a single capsid protein[44]. This sequence is thought to be incapable of replication without the RNA dependent RNA polymerase from MrNV, making this more of a satellite virus “like” virus requiring more research to classify[44]. This is a very substantial finding in this field, as nodaviruses infect both vertebrates, fish, and invertebrates, insects[45]. This revelation of a nodavirus associated satellite virus is an interesting discovery that opens the realm of satellite viruses to different kingdoms[45].

Nilaparvata Lugens Commensal X Virus

In 2005 another satellite virus, Nilaparvata lugens commensal X virus, or NLCXV, was characterized in the brown planthopper *Nilaparvata Lugens*, an insect species that has proved very damaging to agricultural rice fields throughout Asia[14,46,47]. While the application of Imidacloprid, a systemic nitroguanidine insecticide, has helped prevent the destruction of fields by this pest[48]. However, resistance to this drug appeared in various insect species such as the

house fly, Colorado potato beetle, western flower thrips, and others prior to spreading into the brown planthopper[47]. The impact that this insect has had on Asian agriculture emphasizes the importance of research into their viral susceptibilities. NLCXV has been isolated from diseased individuals alongside HiPV, a virus that infects the midgut of the closely related Laodelphax striatellus, or small brown planthopper, and is excreted through feces without causing symptoms[47]. NLCXV is a relatively large satellite virus with a diameter of 30nm and a single stranded RNA genome of 1600 nucleotides associated with three structural proteins of 50, 49, and 43kDa[47]. The genome was analyzed and determined that it contained no coding genes related to replicase activity, which is a common aspect of satellite viruses that further integrates their reliance on helper viruses. The insects from which this study was taken were infected with HiPV and NLRV, the two helper virus suspects[47]. Replication studies deduced that NLCVX replicates vertically, which in association with other findings, such as its 30nm size and lack of replicase activity, suggest that NLCXV may be a new class of satellite virus[47].

Chronic Bee Paralysis Virus Satellite

Other satellite viruses are associated with insects, the most well known of them being the Chronic Bee Paralysis Virus, or CBPV, and its satellite CBPV satellite, which is sometimes referred to as CBPVS or chronic bee-paralysis virus associate, CPVA[15,49]. CBPV is a viral disease of honey bees, *Apis mellifera L*., that can occur in two different types with slightly different symptoms. Type 1 CBPV is visible at any season and produces crawling and trembling bees with the uncommon occurrence of entirely black bees at the entrance of the hive[50]. Type 2 CBPV is often seen in early spring and summer in France. It produces groups of trembling, crawling, flightless bees and entirely black honey bees that often guard the entrance to the hive[50]. Death regularly follows any honey bee infected and showing symptoms of either of these types of CBPV. CPVA is a 17nm particle that is serologically unrelated to its helper virus, CBPV[51,52]. RNA comparison of CBPV and CPVA through electrophoresis and RT-PCR showed five unique RNAs present in CBPV, termed 1, 2, 3a, 3b, and 3c, and three unique RNAs in CPVA, termed A, B, and C[51]. Analysis of these RNAs indicated that 3a, 3b, and 3c may be identical to A, B, and C due to their similarity in size[51]. PAGE analysis distinguished that the components of the CPVA RNAs were different in sequence and secondary structures, but were quite similar to CBPV's 3a, 3b, and 3c RNAs[51]. However, these are shown to be serologically different and packaged differently as well. In an SDGC analysis measuring the production of CBPV and CPVA within pupae showed a varied amount of CPVA between individuals. However, there was an inverse correlation between the proportions of CPVA and CBPV and a proportional correlation between the amounts of 3a, 3b, and 3c RNA produced relative to the multiplication of PCVA[51]. T1 fingerprinting of the CPVA RNA showed some minor correlations to CBPV RNA 2, suggesting that CPVA could have an ancestral connection to its helper virus[51]. While these two viruses are serologically different, the satellite requires the presence of a helper, and the helper does not require the satellite, and only a inconsequential portion of the RNA's show similarities to one another, this satellite holds some similarities in genomic sequences to its helper virus. This suggests that this satellite virus may have evolved from its helper, rather than alongside it, and therefore, may be described as an intermediate satellite virus. It follows the necessary requirements to hold this classification, but also contains remnants of its ancestral ties to CBPV.

Lavidaviridae Family

The satellite viruses discussed thus far include a variation of single stranded, positive and negative sense RNA. The family *Lavidaviridae* includes the discovered double stranded DNA satellite viruses, most of which are virophages. Virophages are satellite viruses that are infective and detrimental to the infectivity and pathogenicity of their helper viruses. While some of the previously identified RNA satellite viruses have been shown to induce changes in their helper expression or infectivity throughout the body, they have not been shown to substantially reduce the pathogenicity of their helper virus. Identified satellite viruses within this family include the Sputnik, Zamilon, Mavirus, and Organic Lake satellite viruses.

The First Virophage

Acanthamoeba polyphaga mimivirus, or APM, was first isolated in 1992 from its algae host, Acanthamoeba polyphaga, in a water cooling tower and is currently the largest virus to date. This discovery gave rise to the discovery of the first virophagic satellite virus, Sputnik, in 2009[17,18,54]. The Sputnik virus is comparatively a very large satellite virus with a 740 Angstrom, 50nm diameter icosahedral capsid with an internal lipid membrane[18]. Structural analysis of the capsids and open reading frames of Sputnik suggests a double jelly-rolled conformation of the capsid protein and no homologous sequences between Sputnik and Mimivirus[18]. This is a divergent find compared to mimivirus's single jelly-folded structure and suggests that the evolution of the Sputnik virus was not a derivation of its helper virus but instead from a separate viral lineage[18]. Though the Sputnik virophage has been discovered within amoeba infected by groups A, B, and C of *Mimivirus*, it has only been isolated from group A of *Mimiviruses* themselves[19]. The Sputnik satellite virus was the first satellite virus in which competitive antagonism was observed with its helper virus[17,18,55]. In a study comparing the growth of the host amoeba A. polyphaga, BABL1, and APM corresponding to differential inoculation, various correlations were observed. Comparing the growth of pathogens following inoculation of APM or APM with Sputnik within the host, a substantial Log 2 decrease in the growth of APM was observed[55]. At the same time, the growth of Sputnik reached the same levels that APM observed during its singular inoculation[55]. Chronic coinfection of APM and BABL1 showed a significant inverse correlation of APM to BABL1 that eradicated the presence of BABL1 at 17 days[55]. Following co-infection including Sputnik, there was a substantial decrease in APM, an increase of BABL1, and a magnitude of Sputnik that was doubled both the concentrations of APM and BABL1[55]. The correlation within this study expressed two important influences Sputnik is thought to have over its helper virus. Initially, the proportional inverse relationship between Sputnik and APM suggests Sputnik induces a decrease in concentration of its helper. Additionally, the co-infection studies showed that the bacterial inhibition provided by APM is severely decreased following the input of the Sputnik satellite virus[55]. These results express Sputnik's ability to impede the virulence of mimivirus.

Virophages

Additional virophages such as the Zamilon, Mavirus, Organic Lake Virophage, and Yellowstone Lake virophages have all been found to have small, double stranded DNA genomes[19,21,23,24,57]. Similarly to Sputnik, the Zamilon virophage specifically targets the *Mimivirus*, however, it has been isolated and shown to multiply within groups B and C[19]. Zamilon completes

in inhibiting *Mimivirus* alongside Sputnik. Mavirus is another virophage which infects the *Cafeteria roenbergensis* virus, or CroV[21,22]. Mavirus has been a focus of study regarding the provirophagic sequences within the protist hosts of CroV. Studies suggest that not only do these organisms contain sequences that perpetuate the virophages capability to inhibit its helper virus from replicating, but also a connection between a virophage-host mutualistic relationship[22]. While this beneficial relationship between virus and host is interesting, this also directs attention to many studies that have identified strong correlations between Mavirus and the Maverick/Polinton transposable elements within eukaryotic cells[21,22]. The virophage is similar to these transposons in host range, length, and gene content, suggesting Mavirus may have been a key factor in the evolution of these eukaryotic transposons[21]. While these virophages have been specifically and extensively studied, other satellite virophages have been identified through metagenomic data analysis and have been collectively dubbed Yellowstone Lake and Organic Lake virophages[23,24,57]. Few studies have been done with these new discoveries aside from genomic analysis to identify many conserved regions between them but that they likely arose from different lineages[23]. Though the discovery of virophages is relatively new, the importance which they hold to the viral ecosystem is immense and the opportunity for humans to utilize them is present.

Discussion

A literary analysis of the known satellite viruses shows not only how diverse and unique satellite viruses are from other infectious viral agents, but also how vastly different each satellite virus is from one another. While satellite viruses share the conserved characteristics that they must require a helper virus to replicate due to the lack of genes to encode a viral capsid, must not be necessary for the helper virus to replicate, and must be genomically separate from their helper virus, the interacts they have with their helper viruses and their hosts vary widely. STMV potentiates the infectivity and symptoms of Tobacco Mosaic virus in some plant species but has little effect on others. Panicum Mosaic Satellite Virus inoculation alongside panicum mosaic virus induces far more severe symptomatic effects in all species of millet and switchgrass affected by this virus. The entire family of satellite viruses *Lavidaviridae* consists of virophages that inhibit the ability of their helper viruses to replicate and therefore, produce pathogenetic effects within their hosts. Satellite viruses have been found to associate with plant, protist, and insect viruses, making them capable of infecting diverse kingdoms of life. Moreso, Mavirus is thought to have played a role in the production of transposons that are currently in eukaryotic genomes.

With such an expansive list of hosts, helpers, and even infectivity throughout the kingdoms of life, it is no surprise that satellite viruses have become disadvantageous for humanity on more than a few occasions. SPMV caused “an economically important disease of St. Augustinegrass in the southern United States”. The prevalence of macrobrachium satellite virus impedes the capacities for farmers in Australia to raise giant freshwater prawn as a reliable source of income[40]. *Nilaparvata Lugens* caused immense destruction of rice crops and thus had a substantial economic impact in Asia[46,47]. Chronic bee paralysis virus associate has contributed to a decrease in honey yields and reduced the overall pollination capacity throughout

Europe[15,49,50,]. The influence satellite viruses have had upon these markets enforces the need for further study of this new form of virus. With additional study, answers regarding viral replication, virus-host relationships, and the designation of if viruses are “alive” may be possible[54].

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