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Ambiguity of Genome Packaging Mechanism in Viruses

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ABSTRACT: Viruses can infect every life form, from plants, bacteria, fungi to humans and other vertebrates. To protect life from various viral diseases, it is necessary to control viruses that generally invade all life forms regularly. Among all the methods to combat viral infections, targeting the genome packaging can give us some potential control strategies against viruses. Genome packaging involves translocation and compaction of negatively charged DNA into the confined space of procapsid. The molecular machinery that executes genome packaging in viruses with outstanding accuracy needs to be explored in details. Although mechanism of genome packaging has been studied thoroughly in bacteriophages and large DNA viruses but details of genome packaging and assembly in plant viruses are unexplored yet. This mini review aims to discuss the components of genome packaging in viruses and review recent breakthroughs in this area, which will help deduce the mechanism of genome packaging among viruses.

Keywords: Genome packaging and translocation, Viruses, Packaging ATPase, ATP.

INTRODUCTION

Genome packaging is a vital step in the life cycle of viruses. By understanding how viruses package their genome will give us some insights into the general biology of viruses (Chelikani *et al*., 2014). Generally, viruses follow two basic modes for packaging virion nucleic acid. The first one is the co-condensation of the nucleic acid with viral capsid proteins to form a virus particle. Viruses with a simple structure like HIV, TMV may self-assemble (Kutulay and Bieniasz 2010; Chelikani *et al.,* 2014). The nucleic acid and capsid proteins bind to each other at the same time. At the end, a capsid will form, and nucleic acid will be trapped inside the hollow capsid. The second one is the translocation of nucleic acid into a preformed procapsid shell which requires ATP (Camacho *et al.,* 2003; Mancini *et al.,* 2004). It is found in eukaryotic viral families such as herpes and tailed dsDNA bacteriophages such as T4, lambda. As we know, the viral genome replicates in the form of a concatamer (multiple copies are joined end to end in a long filament) (Chelkani *et al.,* 2014a). Terminase enzyme identifies cos sites of concatamer and attaches to the replicated concatamer. With the help of ATP hydrolysis, one unit of the viral genome is translocated into a preformed capsid (Al-Zahrani *et al.,* 2009). When ATP binds to terminase, it changes its conformation then terminase attach to DNA and moves inside, so DNA is also pushed inside (Sun *et al.,* 2008). Then after one complete set is translocated, terminase will cut it and detach itself. This terminase, along with the rest of the concatamer, will bind to procapsid (Zhang *et al.,* 2011). Chelikani *et al*. 2014, has proposed a classification system of viruses based on the mechanism of genome packaging employed (Chelkani *et al*., 2014a). This group of scientists have classified viruses into three types based on their packaging mechanism. Majorly all the plant viruses fall under type 1 (Ranjan *et al.,* 2021). Understanding their assembly process can help us control viral infections in plants. Disease control of plants is a significant aspect to sustain our huge population. Bacteriophage comes under type 2 where the genome is transported into procapsid with the help of terminase protein (AL-Zahrani *et al.,* 2009; Hedge *et al.,* 2012; Rao and Black, 2005). Terminase protein has two subunits. One subunit has DNA binding activity and another subunit has ATPase activity, unlike type 3, where single protein packaging ATPase has both the domains. All the giant DNA viruses such as mimivirus, vaccinia virus etc comes under type 3 packaging system (Burroughs *et al*. 2007; Iyer *et al*., 2006). The discovery of such giant viruses (gyrus) larger in size than bacteria has changed our perception of viruses. The packaging mechanism of such viruses has nothing in common with other viruses. Their packaging machinery is similar to prokaryotes. We have attempted to discuss all the three types of packaging mechanisms employed by viruses with suitable examples.

Type 1 Packaging Apparatus: In the classification system proposed by Chelikani *et al.* (2014), plant viruses and some small human viruses with less than 20 kb genome size have been placed under type 1,

characterized by a simple ATP independent packaging system (Chelikani *et al.,* 2014a). However, the detection of CPs with ATPase activity in many plant viruses has changed the type 1 packaging system concept. This discovery made it an interesting system to study. The assembly of virus particles in various genera of plant viruses is a necessary condition for long-distance transmission (Sunpapo, 2013). In the assembly of virion particles, protein subunits interact with the viral nucleic acid. It is a very accurate and carefully planned process (Rao, 2006). As we know that viruses are obligate parasites, they can only replicate inside the host. In plants, viruses enter inside the host with the help of vectors such as nematodes, insects, etc. After reaching the host's cytoplasm, physical separation of the capsid from the viral genome takes place, making the viral genome accessible for transcription. Basically, after uncoating, their genome plant viruses follow the lytic pathway (Catalano 2005; Rao 2006). There is a particular region in the cytoplasm known as the viral factory or replication center. As the name indicates, this is the region where viruses increase their copy number (Buck, 1996; Franckei *et al.,* 1985; Catalano, 2005; Rao, 2006). After increasing their copy number, they undergo transcription and translation, leading to the formation of proteins like capsid protein, movement protein, etc. This capsid protein (CP) recognizes the end of the genome and finally encapsulates the whole genome leading to the formation of the mature virus particle (Catalano, 2005; Rao, 2006). In plant cells, this mature virus particle moves from one cell to another cell through plasmodesmata. Another protein called movement protein (MP) encoded by plant viruses also helps transfer virion particles from one cell to a neighboring cell (Sunpapo, 2013). Genome packaging in most plant viruses occurs in the cytoplasm, where they also have a chance to package cellular RNA. Virus packaging machinery should be able to draw a distinction between host and viral nucleic acid (Franckei *et al.,* 1985; Fox *et al.,* 1998). The capsid's core structural proteins have the facility to differentiate and take out viral nucleic acid from host nucleic acid, which is present in the host's cytoplasm (Franckei *et al*., 1985; Fox *et al*., 1998). This identification results from the recognition of a specific structure or sequence of viral nucleic acid known as the origin of assembly (OAS) or packaging signals (Choi and Rao, 2003). Four types of molecular interactions achieve precise selection and encapsulation of the viral genome. 1) protein-protein interactions, 2) protein-RNA/DNA interactions, 3) sequence-independent RNA/DNA-protein interactions, 4) sequence-dependent RNA/DNA-protein interactions (Rao, 2006). Viral genome has also been observed to be packaged by CPs of other related viruses of the same taxonomic group by genome masking phenomenon (Rao, 2006). As discussed above, CP has the ability to distinguish viral nucleic acid from host nucleic acid. This protein-RNA/DNA interaction is specific. In CPs of several plant RNA viruses, some motifs are found in the N terminal, such as ARM (arginine-rich motif), which have an important role in protein-RNA interaction leading to genome encapsidation (Kjjems *et al.*,1992; Johnson, 2003). The ARM was also detected in lambda bacteriophage, HIV Tat, and Rev. In Bromovirus CP, N terminal ARM is flexible, which aids in protein- RNA interaction. Deletion of N terminal amino acids inhibits packaging (Duggal and Hall, 1993). Apart from these, some other factors like genome configuration, packaging signals, RNA structure, viral replicase also helps in genome packaging and assembly. Based on genome configurations, plant viruses may have a segmented or non-segmented genome. In the case of a segmented genome, they can undergo genetic reassortment among different viral strains and have high rate of mutation (Vriend *et al.,* 1986; Catalano 2005). In a segmented genome, the genome is packaged into more than one virion. A protoplast infection analysis was used to determine genome packaging in the turnip crinkle virus. Examination of many mutant viral RNA encapsidation shows that the 186 nucleotides (nt) region at the 3' end of the CP gene and the 28 nt hairpin loop is the most important factor for viral RNA encapsidation (Qu and Morris, 1997). This provides evidence that specific sequences are involved in packaging. The coat protein basically serves as a chaperone for the genome and provides them ambient interactions required to place dense RNA/DNA inside a stable capsid (Chen *et al*., 1989). Auxillary factors such as transfer RNAs also influence genome packaging. tRNAs act as an adapter and function as a carrier for amino acids at the time of protein synthesis (Jahn *et al.,* 1992). They also act as primers for RNA-dependent DNA synthesis in retroviruses. Some plant virus genera, such as bromovirus, cucumovirus, etc. TLS is found at the 3' end of the genome and initiates replication. Apart from their role in translation and replication, they are also involved in genome packaging. Studies have shown the role of tRNA elements in the assembly of plant viruses (Choi *et al*., 2002; Hema *et al*., 2005; Rao *et al.,* 1989). In brome mosaic virus (BMV), gRNA and sgRNA lacking TLS cannot assemble into mature virion particles when incubated with purified BMV coat protein. Assembly was reclaimed by the addition of 201 nt RNA, including BMV TLS (*Choi et al.,* 2002). Type 1 is further subdivided into type 1A, 1B, and 1C. Viruses that represent type 1A system code CPs with ATPase motifs that extend throughout the polypeptide chain. On the other hand, type 1B and 1C systems lack these motifs and exhibit diversity in the type 1 system. Moreover, phylogenetic trees with CPs of different viruses show that type 1B and 1C fall under the same clade, and type 1A falls under different clades and shows divergent evolution (Ranjan *et al.,* 2021).

1A: These viruses encode ATPase fold in their coat protein. ATP plays a significant role in genome packaging, e.g., Potyvirus, the largest plant virus group. Virions are non-enveloped, filamentous. It has ssRNA with 5' terminal linked protein VPg and 3' poly-A tail. Mutation in the ATPase domain of CP gives rise to deficient virion, indicating their role in genome packaging (Rakitina *et al.,* 2005). Four motifs are found

in the ATPase domain of CPs –Walker A, Walker B, sensor, and arginine finger.

1B: This type of packaging system is ATP independent hence, entirely passive (Burroughs *et al*., 2007; Chelikani *et al.*, 2014). Bioinfo analysis does not show any ATPase motifs on the CPs of these viruses eg., tobacco mosaic virus (TMV). In TMV (ssRNA), MP 30 kDa and CP 17.6 kDa are synthesized by subgenomic RNA. In TMV, the proteins assemble around the RNA genome, which becomes trapped inside the hollow capsid. It does not need ATP; hence It is energy independent. There are several packaging signals at the end of the genome, which is identified by CP, and CPs nucleate over it, leading to the assembly of the virion. The distinctive packaging signal or origin of assembly (OAS) such as stem loop-like structure, 3't-RNA like sequence (TLS), and 5' UTR at the genome end identified by CPs help to differentiate viral RNA from cellular RNA (Choi and Rao, 2003; Dreher, 1999). Three hairpin loops are involved in the assembly of TMV. During assembly, coat protein first binds to the 3' end loop. Removal of this loop terminates packaging (D.R Turner and P J Butler, 1986). Another example of type 1B is the human immunodeficiency virus (HIV). The gag protein of HIV-1 is necessary for the assembly of virus particles. Viral genome packaging is initiated by binding gag protein to viral RNA, which occurs in the cytoplasm where gag appear as dimmers. C terminal domain of capsid is essential for Gag-RNA interactions. Gag –viral RNA complex is recruited to the plasma membrane where gag multimerization occurs, and assembly is completed. (Kutluay and Beiniasz, 2010).

1C: In this type of packaging system, along with CPs, ATP hydrolysis is carried out by accessory ATPase such as Hsp 70, P4 ATPase, P10 ATPase, which are recruited at the site of virus assembly (Nair and Savithri, 2009; Verchot, 2012; Gorovits *et al*., 2013). In geminivirus (ssDNA), Rep initiates a rolling circle mechanism. Once DNA is replicated, newly formed DNA participates in the same cycle of events until viral DNA reaches a certain threshold level. The interaction of CP with Rep and the ATPase activity of Rep has a crucial role in genome packaging (Malik *et al*., 2005; Selth *et al.,* 2005).

Type 2 Packaging Apparatus: This type of packaging system is common to bacteriophages such as T4, lambda. In the case of T4 bacteriophage, the end product of replication is the branched concatamer genome. Packaging is accomplished by terminase protein, which recognizes the extreme end of the genome and docks the DNA to the portal situated at the vertex of the prohead. The final assembly takes place with the help of ATP hydrolysis. Terminase has two subunits – small subunit gp16 has DNA binding activity, and large subunit gp17 has ATPase activity (Al-Zahrani *et al.,* 2009; Hedge *et al*., 2012; Rao and black 2005). Gp 16 recognize the pac sites present at the genome termini and oligomerize itself then gp17 bind to it. With the help of ATP, the hydrolysis genome is being translocated, and then accessory proteins like tail fibers come and attach, leading to the formation of the complete virion particle.

Another example is of lambda phage, having ds DNA and genome size of 48.5 kb. When a virus adheres on the surface of the host, it will deliver its genome, which has cos sites. Cos sites have sticky ends, so cos sites will circularize themselves. At first, they opt for the theta mode of replication. Later they switch from theta mode to rolling circle replication to produce more copy numbers. Terminase enzyme will come and attach at the end of the genome, and with the help of ATP hydrolysis, the genome will be transported inside the prohead. The mechanism of genome packaging in lambda phage is briefly described in three steps below.

1. Initiation: lambda concatamer has cos region, which contains several R units recognized by gpNu1 (small subunit of lambda phage). Terminase assembly occurs at cos B. interaction of gpNu1, and cos B is responsible for dimeric assembly of gpA (large subunit of lambda terminase). Then the duplex is being cut at the cos N site. Later the strands separate due to the helicase activity of gpA. The energy required for strand separation is supplied by ATP hydrolysis in the presence of Mg2+. ATP regulates the assembly of terminase subunits (Yang *et al.,* 1997; Yang and catalano, 2004). Strand separation releases the right end of the chromosome, leaving the left end, which is still attached to terminase assembly.

2. Translocation: gpF1 and IHF have a significant role in translocation. they are essential for cos clearance. gpF1 protein is made during the lytic cycle, and it helps in cos clearance. IHF is an E.coli integration host factor that bends DNA at 180 degree (Kosturko *et al*., 1989; Rice *et al*., 1996). It modulates lambda development in vivo and it has been observed that in vitro DNA packaging is lowered in its absence (Yang and Catalano, 2003; Hwang and Feiss, 1995). After cos clearance, DNA is docked inside the procapsid with the help of ATP hydrolysis. Once DNA is transported inside the capsid, the volume of capsid increases which leads to enlargement of its size (H. Murialdo, 1991). Capsid obtains an icosahedral shape. The viral protein gpD comes and attaches to the capsid and makes sure that DNA does not come out of it (Dokland and Murialdo 1993; Perucchetti *et al.,* 1988; Imber *et al.,* 1980; Sternberg and Weisberg, 1977).

2. Termination: Cos Q plays an important role in termination (Cue and Feiss, 2001). It promotes the terminase complex to the cos N sites. If there is a mutation in cos Q, then translocation will not stop. After the cleavage reaction at the cos N site, terminase proteins attached to the portal of DNA-filled capsid will dissociate and bind to the end of the next genome in the concatemer.

Type 3 Packaging Apparatus: Giant viruses like Mimivirus, Pandoravirus fall under this category which consist of viruses with ATP dependent genome packaging machinery. Studies suggest that the mechanism of genome packaging in these viruses is similar to prokaryotes rather than other well-known viruses (Chelikani *et al*., 2014). As we know that the end product of prokaryotic genome replication is concatenated genome. At the end of the genome, there is a KOPs sequence and a dif site. This is the site where

ATPase, recombinase, and topoisomerase interact and work collaboratively (Perals *et al.*, 2001; Deiber *et al*., 2001; Aussel *et al.*, 2002). They untangle the genome, and finally, the genome is docked inside. Components of genome packaging machinery in prokaryotes (bacteria and archaea) which are also present in Nucleocytoplasmic large DNA virus (NCLDV), are as follows-

1. Packaging ATPase: ATPase in NCLDVs has parallels with prokaryotic FtsK/HerA motor rather than other viruses (Iyer *et al*., 2004). It is needed to transport the genome.

2. Type 2 topoisomerase: It is required to separate daughter DNA molecules. After replicating a circular chromosome, the resulting daughter DNA molecule remains linked together as catenanes. To segregate these chromosomes into daughter cells, the two circular DNA molecules must be disengaged from each other. This separation is accomplished by type 2 topoisomerase (Champoux *et al*., 2001). These enzymes have the ability to break a double-stranded DNA molecule through this break. This reaction can easily decatenate the two circular daughter chromosomes by breaking one DNA circle and passing the second through the break, allowing their segregation into separate cells.

3. Recombinase: Catalyze site-specific recombination. Most recombinases fall into two categories – a) tyrosine recombinase, which breaks and rejoin single strands in pairs to form a holiday junction intermediate b) serine recombinase, which cut both strands. NCLDVs exhibit only serine recombinase, whereas bacteria have both types of recombinases (Grindley *et al*., 2006; Aussel *et al*., 2002; Pérals *et al.*, 2001).

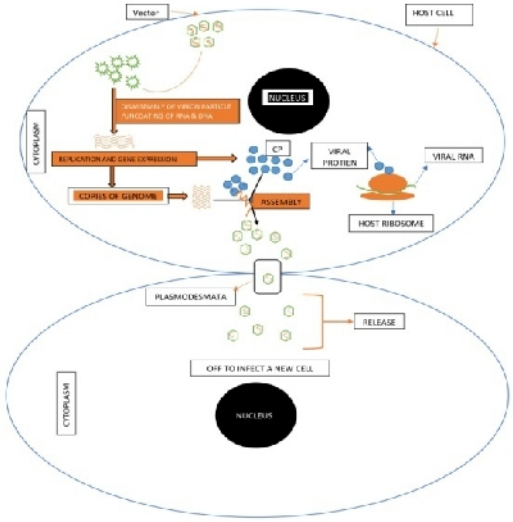

Fig. 1. Assembly and genome packaging in type I system with plant virus as a prototype.

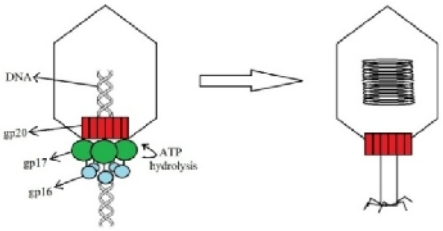

Fig. 2. Genome packaging in viruses belong to type II system.

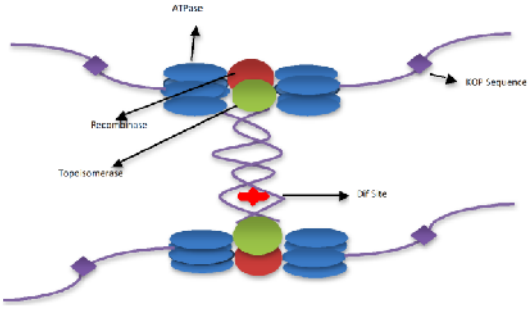

Fig. 3. Packaging machinery in prokaryotes and type III packaging system.

CONCLUSION

It appears that the packaging of the viral genome can be classified into three types. As seen in the case of small plant viruses where the packaging mechanism is further classified into subgroups based on the variations observed. It ranges from simple as in the case of type 1B and 1C to more complex ATP-dependent type 1A. In type 2 system, packaging of viral genome involves terminase assembly at cos site of the concatamer and nicks the duplex leaving the left end of the genome to be packaged. After binding to procapsid, packaging machinery docks the DNA inside the capsid through portal protein present at the vertex. In type 3, packaging machinery is phylogenetically closer to prokaryotes. It also suggests that the viral packaging mechanism has a vital role in the coevolution of bacteria. We have attempted to discuss all the three types of packaging mechanisms employed by viruses with suitable examples.

FUTURE SCOPE

All known viruses ranging from smallest to largest use at least three different basic mechanisms to accomplish their genome packaging. The presence of three basic types of viral packaging systems probably indicates independent innovations. Here, we have made an attempt to classify viral packaging systems into three large groups and, based on variations within these groups, into several subgroups. Although mechanism of genome packaging has been studied thoroughly in viruses belongs to type I and II but details of genome packaging and assembly in plant viruses are yet to be explored. Our lab is trying to unravel the secret of genome packaging in plant viruses by considering potexvirus and geminivirus as a prototype. We believe that our proposed classification of viral packaging systems will help us to better understand packaging mechanisms.

Conflict of Interest. The authors have declared no competing interests exist.

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