

Negative Strand RNA Virus Nucleocapsid

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The nucleocapsid of negative strand RNA virus (NSV) is a linear protein-RNA complex that is the template for the viral RNA-dependent RNA-polymerase. The structure of the nucleocapsid protein from all NSVs shares a core motif that is suitable for assembling the linear nucleocapsid. The unique structure of the nucleocapsid allows it to encapsidate the viral RNA genome for virion assembly, and at the same time serve as the template for viral RNA synthesis.

Keywords: nucleocapsid ; negative strand RNA virus ; 5H+3H motif ; linear assembly ; protein-RNA complex ; template ; viral RNA synthesis ; RNA-dependen RNA polymerase ; codon usage bias ; gene junction

1. Definition

Negative strand RNA viruses (NSVs) include many important human pathogens, such as influenza virus, Ebola virus, and rabies virus. One of the unique characteristics that NSVs share is the assembly of the nucleocapsid and its role in viral RNA synthesis. In NSVs, the single strand RNA genome is encapsidated in the linear nucleocapsid throughout the viral replication cycle. Subunits of the nucleocapsid protein are parallelly aligned along the RNA genome that is sandwiched between two domains composed of conserved helix motifs. The viral RNA-dependent-RNA polymerase (vRdRp) must recognize the protein–RNA complex of the nucleocapsid and unveil the protected genomic RNA in order to initiate viral RNA synthesis. In addition, vRdRp must continuously translocate along the protein–RNA complex during elongation in viral RNA synthesis. This unique mechanism of viral RNA synthesis suggests that the nucleocapsid may play a regulatory role during NSV replication.

2. Introduction

All viruses assemble a nucleocapsid. The capsid consists of viral proteins and encloses the nucleotide genome of the virus. The word “capsid” is originated from the Latin *capsa* (box). The primary function of the capsid (also known as “protein coat” or “protein shell”) is to carry and protect the viral genome during transmission between cells. The term “nucleocapsid” refers to the capsid protein–nucleotide complex. For efficiency, the viral nucleocapsid is assembled by organization of capsid protein subunits following a geometric symmetry, including the icosahedral symmetry for spherical viruses and the helical symmetry for filamentous viruses (read Chapter 3 in Fields Virology for details) ^[1]. For negative strand RNA viruses (NSVs), the nucleocapsid has a unique structure that is pertinent to its functions in the virus replication cycle. This review will discuss the assembly of the NSV nucleocapsids and the structure–function relationship.

According to International Committee on Taxonomy of Viruses (ICTV), NSVs belong to Phylum *Negarnaviricota*, Realm: *Riboviria* ^{[2][3]}. Since 2003, the structure of the nucleocapsid or the capsid protein has been determined for at least 21 genera in *Negarnaviricota* (Table 1). The determined structures have confirmed a genetic relationship among members of different NSV families. Common folds of the NSV capsid proteins and principles of nucleocapsid assembly have emerged, and the functional role of the nucleocapsid in the unique NSV viral RNA synthesis has also become clearer. It is because of this role that additional examination of the structure of NSV nucleocapsids has now become essential for further understanding of NSV replication and pathogenesis.

Table 1. Reported nucleocapsid structure of members from Phylum *Negarnaviricota*.

Family	Subfamily	Genus	Name	(PDB Code)
Subphylum:Haploviricotina;Class:Monjiviricetes;Order:Mononegavirales				
<i>Bornaviridae</i>		<i>Mammalian 1 orthobornavirus</i>	Borna disease virus (BoDV)	(1N93) ^[4]

Family	Subfamily	Genus	Name	(PDB Code)
<i>Filoviridae</i>		<i>Ebolavirus</i>	Ebola virus (EBOV)	(4Z9P) ^[5]
		<i>Marburgvirus</i>	Marburg virus (MARV)	(5F5M) ^[6]
<i>Paramyxoviridae</i>	<i>Avulaviridae</i>	<i>Avian orthoavulavirus 1</i>	Newcastle disease virus (NDV)	(6JC3) ^[7]
	<i>Orthoparamyxoviridae</i>	<i>Henipavirus</i>	Nipah virus (NiV)	(4CO6) ^[8]
		<i>Morbillivirus</i>	Measles virus (MeV)	(4UFT) ^[9]
	<i>Rubulaviridae</i>	<i>Orrthorubulavirus</i>	parainfluenza virus 5 (PIV5)	(4XJN) ^[10]
<i>Pneumoviridae</i>		<i>Metapneumovirus</i>	Human metapneumovirus (hMPV)	(5FVC) ^[11]
		<i>Orthopneumovirus</i>	respiratory syncytial virus (RSV)	(2WJ8) ^[12]
<i>Rhabdoviridae</i>		<i>Lyssavirus</i>	Rabies virus (RABV)	(2GTT) ^[13]
		<i>Vesiculovirus</i>	Vesicular stomatitis virus (VSV)	(2GIC) ^[14]
Subphylum:Polyploviricotina;Class:Ellioviricetes;Order:Bunyavirales				
<i>Arenaviridae</i>		<i>Mammarenavirus</i>	Lassa Virus (LASV)	(3T5Q) ^[15]
<i>Hantaviridae</i>	<i>Mammantaviridae</i>	<i>Orthohantavirus</i>	Andes virus (ANDV)	(5E04) ^[16]
			Hantaan virus (HTNV)	(6I2N) ^[17]
<i>Nairoviridae</i>		<i>Orthonairovirus</i>	Crimean-Congo Hemorrhagic Fever Virus (CCHFV)	(4AKL) ^[18]
			Hazara virus (HAZV)	(4XZE) ^[19]
			Kupe virus (KUPV)	(4XZC) ^[19]
			Erve virus (ERVEV)	(4XZ8) ^[19]
<i>Peribunyaviridae</i>		<i>Orthobunyavirus</i>	Bunyamwera virus (BUNV)	(4IJS) ^[20]
			La Crosse virus (LACV)	(4BHH) ^[21]
			Leanyer orthobunyavirus (LEAV)	(4J1G) ^[22]
			Schmallenberg virus (SBV)	(4JNG) ^[23]
<i>Phenuiviridae</i>		<i>Phlebovirus</i>	Rift Valley Fever Virus (RVFV)	(4H5P) ^[24]
			Toscana virus (TOSV)	(4CSF) ^[25]
			Severe fever with thrombocytopenia syndrome virus (SFTSV)	4J4R) ^[26]

Family	Subfamily	Genus	Name	(PDB Code)
<i>Tospoviridae</i>		<i>Orthotospovirus</i>	Tomato spotted wilt tospovirus (TSWV)	(5IP3) [27]
Subphylum: <i>Polyploviricotina</i> ; Class: <i>Insthoviricetes</i> ; Order: <i>Articulavirales</i>				
<i>Orthomyxoviridae</i>		<i>Alphainfluenzavirus</i>	Influenza A virus (IFAV)	(2IQH) [28]
		<i>Betainfluenzavirus</i>	Influenza B virus (IFBV)	(3TJ0) [29]
		<i>Deltainfluenzavirus</i>	Influenza D virus (IFDV)	(5N2U) [30]
		<i>Isavirus</i>	Infectious Salmon Anemia Virus (ISAV)	(4EWC) [31]
	Class: <i>Tymovirales</i> *; Order: <i>Alphaflexiviridae</i>			
			Papaya mosaic virus (PapMV)	(4DOX) [32]
		<i>Potexvirus</i>	Pepino mosaic virus (PepMV)	(5FN1) [33]

3. The Capsid Protein Fold

The Phylum *Negarnaviricota* has been divided into two Subphyla; *Haploviricotina* and *Polyploviricotina*. The distinction between the two Subphyla is the nonsegmented or segmented nature of the viral genome. The NSVs are then further classified phylogenetically ultimately yielding a separation by virion morphology. Although these viruses can differ greatly in their global structures, structural and functional similarities are observed when comparing their capsid proteins.

The capsid proteins (N) of NSVs share a common fold. As shown for vesicular stomatitis virus (VSV) in Figure 1A, the N-terminal lobe and the C-terminal lobe are connected by a single polypeptide chain [14]. The core of the capsid protein consists of five α -helices in the N-terminal lobe (5-H motif) and three α -helices in the C-terminal lobe (3-H motif) [34]. When the protein subunit is assembled into the nucleocapsid, the encapsidated RNA is situated between the two lobes. The observation of a conserved structural motif present in all nucleocapsid proteins in NSVs is analogous to that a β -barrel fold is observed in the capsid proteins of spherical viruses [35].

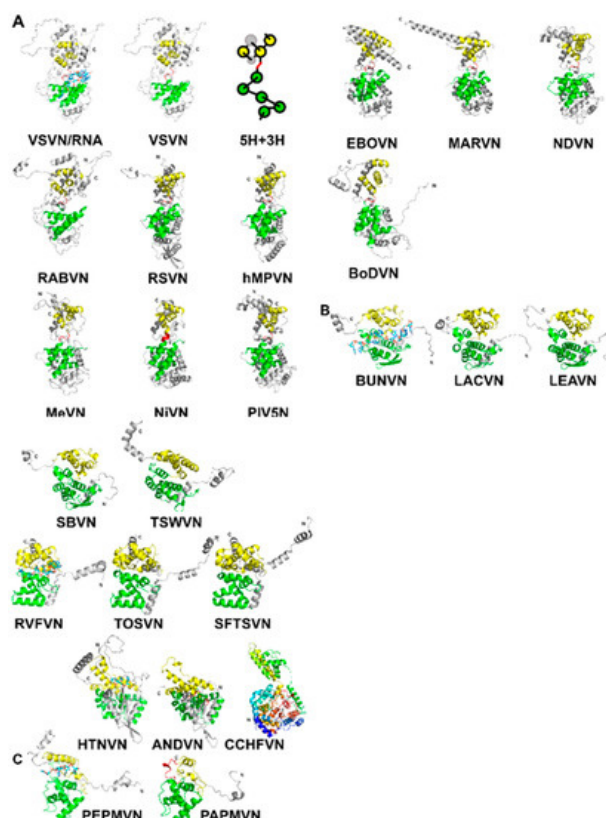


Figure 1. (A) A ribbon drawing of VSV nucleocapsid protein (VSVN) in complex with 9 nucleotides (sticks) encapsidated. The 5H in the N-lobe is colored green, and 3H in the C-lobe is colored yellow. Termini are labeled as N and C, respectively. The linker between the two lobes is colored red. The same ribbon drawing without RNA is shown to the right. Ribbons drawings in this and the following figures are prepared with PyMol [40]. A cartoon is drawn to illustrate the 5H+3H motif. Ten other related N structures in Table 2 are also shown using the same color scheme. **(B)** Eleven N structures in *Polyplaviricotina* are shown, with those from BUNV (BUNVN), RVFV (RVFVN), and HTNV (HTNVN) in complex with encapsidated nucleotides (sticks). The N-domain in the N core is colored green and the C-domain in the N core is colored yellow. Structures of closely related N proteins according to Table 3 and Table 5 are grouped together. The structure from CCHFV (CCHFVN) is colored rainbow from the N-terminus (blue) to the C-terminus (red) because no clear N- and C-domains could be identified. **(C)** Two structures from the +ss RNA viruses are shown, with that from PepMV (PepMVN) in complex with encapsidated RNA. The color scheme is the same as in **(B)**.

The two largest NSV orders contain the majority of known capsid protein structures are *Mononegavirales* and *Bunyavirales*. Beyond these, there are a small number of structures from *Articulavirales* represented by the segmented *Orthomyxoviruses*. Structures from the order *Alphaflexiviridae* are included in this review because of structural similarities, even though these are positive single strand RNA viruses.

The structures of *Haploviricotina* capsid proteins from 11 members in the order *Mononegavirales* were superimposed using the program Fr-TM-align [36] (Table 2). Large variance in capsid protein Size is observed in known structures with MWs ranging from 41 kDa in BoDV up to 83.3 kDa in EBOV; however, the capsid cores maintain structural homology. Similarities among these structures are essentially the same as previously observed [34][37]. It is well expected that viruses in the same family have a high structural similarity in their capsid proteins, such as VSV and RABV; RSV and hMPV; PIV5, MeV, NiV, and NDV; EBOV and MARV (Figure 1A). However, the observed similarity between NDV and MARV appears to be an exception (Table 2). The nucleocapsid structure of MARV is very close to that of EBOV. The apparent more favorable alignment for MARV could be due to that less residues are included in the structure of MARV nucleocapsid protein.

Table 2. Structural Comparison of *Mononegavirales* Nucleocapsids.

	RABV	RSV	hMPV	PIV5	MeV	NiV	NDV	EBOV	MARV	BoDV
VSV	2.63/96 *	5.07/79	5.17/81	5.34/78	5.30/79	4.73/83	5.20/75	5.18/82	4.20/85	5.09/78
RABV		5.01/76	4.93/78	5.04/73	5.06/76	4.27/81	5.11/73	4.38/78	5.01/82	5.03/75
RSV			1.40/100	4.35/91	4.35/91	4.90/93	4.36/91	4.39/87	4.85/86	4.83/80
hMPV				4.10/94	4.20/94	4.79/92	4.24/94	4.48/89	4.11/90	4.36/78
PIV5					2.47/97	3.59/100	1.82/98	4.87/89	3.77/94	4.51/83
MeV						3.26/97	2.32/98	4.43/87	3.97/94	4.41/81
NiV							3.38/99	4.12/92	3.62/91	5.19/80
NDV								4.79/89	3.92/96	4.76/84
EBOV									1.87/99	5.53/83
MARV										5.47/84

For *Polyplaviricotina* NSVs, homology is only present among members in the same family (Table 3 and Table 4). However, the fold of the capsid proteins shares some common features with those from members in *Mononegavirales*. The most apparent similarity is that the encapsidated genomic RNA is also sandwiched between the N- and C-terminal lobes (Figure 1B).

Table 3. Structural Comparison of *Bunyavirales* Nucleocapsids.

	LACV	LEAV	SBV	TSWV	TOSV	SFTSV
BUNV	2.11/98	1.87/100	2.07/100	3.68/87	-	-
LACV		2.07/94	2.09/93	3.64/85	-	-
LEAV			1.66/99	3.96/89	-	-

	LACV	LEAV	SBV	TSWV	TOSV	SFTSV
SBV				3.52/88	-	-
RVFV					1.88/91	1.83/90
TOSV						2.65/94

Table 4. Structural Comparison of Other Nucleocapsids.

	HTNV	HAZV	KUPV	ERVEV	IFBV	IFDV	ISAV	PepMV
ANDV	1.94/95	-	-	-	-	-	-	-
CCHFV		1.77/100 [†]	1.90/99	1.56/91	-	-	-	-
HAZV			1.56/97	1.32/89	-	-	-	-
KUPV				1.27/87	-	-	-	-
IFAV					2.29/95	3.21/94	3.49/84	-
IFBV						3.02/93	3.36/78	-
IFDV							3.58/76	-
PapMV								2.06/93

Further examination reveals that the 5-H and 3-H motifs share the same topology, but the orientations of the helices are often different. For members in *Peribunyaviridae* and *Tospoviridae*, the N-terminal lobe contains the same 5-helices and may be superimposed with that from members in *Mononegavirales* (Table 5). For the C-terminal lobe, on the other hand, the first two helices in the 3-H motif could be superimposed with those from members in *Mononegavirales* while the third α -helix takes a reverse orientation. For *Bunyaviridae* members in *Phenuiviridae*, *Nairoviridae*, and *Hantaviridae*, the helices in the N-terminal 5-H motif have large differences in their orientation despite the same topology. Their N-terminal lobes could not be superimposed with those from members in *Mononegavirales*. The same situation is found in the C-terminal 3-H motif. However, the fold in the C-terminal lobe from members in *Nairoviridae* and *Hantaviridae* is homologous to that from members in *Peribunyaviridae*, except for the orientation of the last α -helix (Table 5).

Table 5. Structural Comparison of Representative Nucleocapsid Lobes.

	VSV-N [‡]	CCHFV-N	HTNV-C
BUNV-N	4.77/82	3.77/82	
BUNV-C			2.88/87
PepMV-N	3.28/61		

Finally, the size of the RNA cleft in a N subunit may vary widely in these viruses. The C-terminal lobe from members in *Bunyavirales* has much less separation from the N-terminal lobe so that the cleft between the two lobes is much narrower than that from members in *Mononegavirales*. This narrowing of the RNA cleft results in a very shallow pocket in which the RNA resides in a fissure rather than within a deep cavitation [21]. Differences in these structural features may allow more a flexibility in supramolecular nucleocapsid morphology to package the segmented genomes that are incorporated stochastically during virion assembly [38][39].

For members in *Orthomyxoviridae*, direct structural comparison of the nucleocapsid proteins with other families is not informative; two terminal lobes are visible, but the division is not completely clear because no information of RNA encapsidation is available [28].

In addition to NSVs, the structure of nucleocapsid proteins from members in *Alphaflexiviridae* is included in the comparison even though they are positive single strand RNA viruses [32][33]. They contain similar N- and C-terminal lobes that encapsidate the genomic nucleotide between them (Figure 1C). Some of the bases in the RNA strand are stacked and face the exterior of the nucleocapsid, whereas some face the interior. The N-terminal domain of their N proteins is

homologous to that of NSV N proteins (Table 5). This suggests that the strategy to assemble a linear nucleocapsid is common in both negative and positive single strand RNA viruses, and the same structural features in the capsid protein are essential for the encapsidation of the linear nucleotide in the nucleocapsid.

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