Architecture and regulation of negative-strand viral enzymatic machinery

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Negative-strand (NS) RNA viruses initiate infection with a unique polymerase complex that mediates both mRNA transcription and subsequent genomic RNA replication. For nearly all NS RNA viruses, distinct enzymatic domains catalyzing RNA polymerization and multiple steps of 5' mRNA cap formation are contained within a single large polymerase protein (L). While NS RNA viruses include a variety of emerging human and agricultural pathogens, the enzymatic machinery driving viral replication and gene expression remains poorly understood. Recent insights with Machupo virus and vesicular stomatitis virus have provided the first structural information of viral L proteins, and revealed how the various enzymatic domains are arranged into a conserved architecture shared by both segmented and nonsegmented NS RNA viruses. In vitro systems reconstituting RNA synthesis from purified components provide new tools to understand the viral replicative machinery, and demonstrate the arenavirus matrix protein regulates RNA synthesis by locking a polymerase-template complex. Inhibition of gene expression by the viral matrix protein is a distinctive feature also shared with influenza A virus and nonsegmented NS RNA viruses, possibly illuminating a conserved mechanism for coordination of viral transcription and polymerase packaging.

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Introduction

Viruses are the only organisms known to store their genetic information solely in the form of RNA, and have thus evolved unique machinery to replicate an RNA genome and initiate viral gene expression in the infected cell. The Large polymerase protein (L) of negative-strand (NS) RNA viruses is a particularly intriguing model, where all of the enzymatic activities required for mRNA transcription, RNA modification and genomic RNA replication are contained within a single polypeptide. Whereas the host cell and many other viruses require a suite of enzymes to accomplish these tasks, L alone is the catalytic engine driving NS RNA viral replication.

Combined with the unique biology of L proteins, NS RNA viruses include many emerging human and agricultural pathogens.[1-3] Continuous transmission of NS RNA viruses—including rabies virus, measles virus and respiratory syncytial virus—is coincident with sporadic outbreaks of hemorrhagic fever NS RNA viruses such as Machupo virus, Lassa virus and Ebola virus. Moreover, newly discovered NS RNA viruses continue to emerge, with recent identification of severe fever with thrombocytopenia syndrome virus in Asia (2011),[4] Chapare virus and Lujo virus as new agents of hemorrhagic fever in South America and Africa (2008/2009),[5,6] and Schmallenberg virus infection of livestock in Europe (2011/2012).[7] As NS RNA viruses continue to grow in health and economical importance, the catalytic activities of L will become increasingly critical as potential therapeutic targets.

Mechanistic studies of L structure and function require development of tractable in vitro techniques and direct analysis of RNA products. Recently, structural insights into L proteins from two distantly related NS RNA viruses have revealed the overall architecture of this multifaceted enzyme and determined

how the various enzymatic domains of L are arranged into a single protein.[8,9] The development of recombinant RNA synthesis systems utilizing full-length L and purified components has provided new insight into regulation of NS RNA viral replication,[10-13] and offers further opportunity to interrogate NS RNA viral biology and develop rationally designed antiviral inhibitors.

L Protein Architecture and Domain Organization

The replication machinery of all NS RNA viruses is built upon an evolutionarily related RNA-dependent RNA polymerase domain that shares phylogenetic conservation with the polymerase from positive-sense and double-strand RNA viruses.[14,15] All of the NS RNA viral polymerase machinery is retained within the single L protein, with the exception of influenza A virus and members of the *Orthomyxoviridae* family where the polymerase is broken into a tripartite complex. The corresponding smaller polymerase fragments have facilitated studies on the influenza virus replicative proteins,[16-18] and enabled a greater biochemical and structural understanding of the tripartite complex (discussed in detail below). Conversely, functional characterization of NS RNA viral L proteins has been impeded by their large size (~250 kDa) and the presence of flexible domains or connecting "hinge" regions. Hinge regions are believed to separate independent enzymatic activities;[19] but regulatory interactions between the distinct activities indicate the overall organization of L is critical for proper enzymatic function.[20-22] In spite of this importance, the structural architecture of L proteins has remained a mystery.

Blocks of phylogenetically conserved domains have been identified within the amino acid sequence of *L* genes.[19] The hallmark presence of fingers, palm and thumb subdomains shared by all known polymerases allowed identification of the RNA-dependent RNA polymerase domain,[14] which was later verified by mutations to a catalytically essential motif predicted to form a divalent cation coordination site.[23-25] Further genetic and biochemical studies implicated additional conserved regions involved in template recognition, cofactor association and formation of the 5' mRNA cap structure during viral transcription.[11,26-29]

While all L proteins share a phylogenetically conserved RNA-dependent RNA polymerase domain, the L proteins of segmented and nonsegmented NS RNA viruses differ in the conserved domains associated with cap formation (**Fig. 1**). Segmented viruses, including the tripartite influenza virus polymerase, recognize host mRNAs[30] and cleave off the 5' mRNA cap with a conserved endonuclease activity.[31-34] The host mRNA cap is then used to directly prime viral mRNA transcription such that the viral mRNAs are capped with stolen host 5' sequence in a process termed "cap-snatching."[35] In contrast, most nonsegmented viruses directly synthesize their 5' cap structure using a mechanistically unparalleled 5' polyribonucleotidyl-transferase activity (PRNTase)[11,36] and a dual-specificity guanine-N7 and 2'-O methyltransferase (MTase).[37-39]

The structural organization of each type of L protein was investigated using single-particle electron microscopy (EM) and recombinant L that maintains functional RNA synthesis activity in vitro.[8,9] The architecture of L was compared between Machupo virus (MACV), a cap-snatching segmented virus of the *Arenaviridae* family, and vesicular stomatitis virus (VSV), a nonsegmented virus of the *Rhabdoviridae* family that performs de novo cap-synthesis. The corresponding EM class averages revealed a shared architecture where L consists of a central ring-like RNA-dependent RNA polymerase domain upon which divergent appendages dedicated to the distinct 5' mRNA capping activities are attached (**Fig. 1**).[8,9] The EM maps confirmed that L consists of discrete domains, and demonstrated that the shared conserved function (polymerase) relates to a shared architecturally conserved domain (central ring). Correspondingly, the divergent 5' capping functions (MACV cap-endonuclease vs. VSV PRNTase/MTase) relate to divergent, architecturally distinct domains (MACV large arm-like appendage vs. VSV large globular appendage) (**Fig. 1**).

Structural insight into MACV and VSV L also revealed a large degree of conformational flexibility between the ring-like polymerase and cap formation appendages.[8,9] Observed alternative orientations of the capping domains agrees with the previous prediction of flexible hinge regions linking distinct enzymatic activities.[19] Hinge regions are remarkably tolerant to domain insertion, and fluorescent reporter sequences have been successfully introduced within several L proteins without compromising catalytic function or virus viability.[40-42] Therefore, flexible hinge regions not only maintain the modular architecture of L, but may also play an additional role in preserving functional plasticity of the NS RNA viral polymerase complex and facilitating viral evolution.

The RNA-dependent RNA polymerase domain of MACV and VSV L appears as a closed ring with a hollow stain-collecting center,[8,9] and this architectural organization parallels the caged appearance to the reo- and rotavirus dsRNA viral polymerases.[43,44] Enclosure of the reovirus RNA-dependent RNA polymerase active site results from an N-terminal bridging domain and a carboxyl-terminal "bracelet" domain. These bracketing domains have been implicated in enhancing polymerase processivity and forming a unique secondary RNA exit tunnel to facilitate positive-sense transcript release.[45] L and the reovirus polymerase complex have dual functions as an mRNA transcriptase and an RNA replicase, and a similar four-tunnel architecture may be required by negative-sense RNA viral polymerases to separate template and replication RNAs for independent nucleoprotein encapsidation.

Further insight into the low-resolution maps of L can be gained through comparison with structural analyses of the influenza virus polymerase complex. Although the influenza virus polymerase is a heterotrimeric complex of three subunits (PA, PB1 and PB2), the tripartite polymerase is also ~250 kDa and is closely related to NS RNA viral L proteins (**Fig. 1**). Pioneering EM studies with influenza virus provided the first structural information for a recombinant NS RNA viral polymerase complex,[46] and

considerable progress has since resulted in an ~18 Å resolution 3D reconstruction suitable for initial quasi-atomic modeling of fragments of the individual polymerase subunits.[47] Compared with the core structure of MACV and VSV L, the influenza virus polymerase exhibits a similar overall structural shape and central hollow architecture.[47,48] However, the influenza virus polymerase adopts a more compact structure that lacks the large flexible appendage observed in 2D EM analysis of MACV and VSV L (**Fig. 1**). The compact architecture of the influenza virus polymerase can be partially explained by conformational changes induced upon interaction with the viral genomic RNA termini. The soluble RNA-free form of the influenza virus polymerase adopts a more open architecture compared with the RNA-bound or N-RNA associated isoforms and conformational rearrangements have been proposed to involve movement of the N-terminal domain of PB2.[47-49] The large appendage of VSV L undergoes a dramatic rearrangement upon association with the viral phosphoprotein, indicating that similar conformation changes can occur within the capping domains of L proteins.[9] These changes may represent different functional states within NS RNA viral polymerases, and support the hypothesis that flexibility between domains dedicated to RNA synthesis and cap formation is required to facilitate alternate functionality in mRNA transcription and genomic RNA replication.

3D reconstruction and subunit localization revealed that in addition to their functional roles during cap formation, the influenza virus PA and PB2 subunits are structurally important to bracket the core PB1 polymerase domain structure.[47,50,51] Similarly, N-terminal portions of the VSV L capping domains are required to complete the central ring structure.[9] Therefore, the domains primarily thought to be involved in cap formation are likely additionally required to enclose the RNA-dependent RNA polymerase active site and may explain the importance of intramolecular L-L interactions evolutionarily conserved in segmented and nonsegmented L proteins.[52,53]
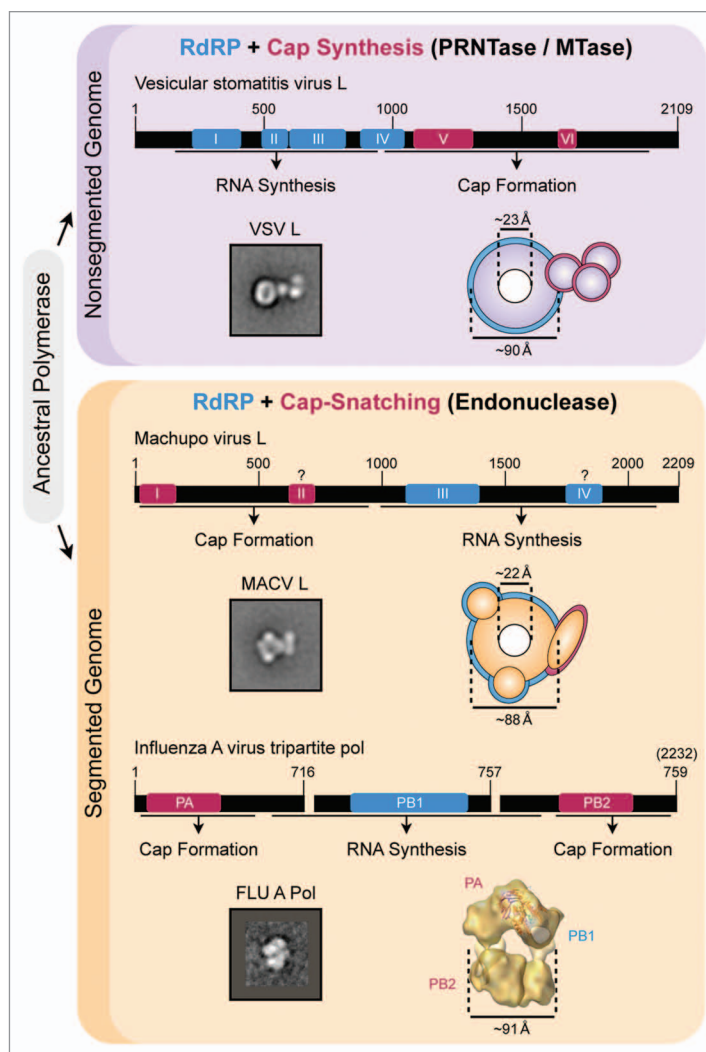

Figure 1. Structural architecture and organization of NS RNA viral polymerases. Conserved architecture and domain organization found in nonsegmented (top, purple) and segmented (bottom, orange) polymerases. The linear amino acid sequence of L and the tripartite influenza virus polymerase contain highly conserved regions dedicated to RNA synthesis (blue boxes). L and the influenza virus polymerase also contain blocks of conservation dedicated to 5' cap formation (maroon boxes), including an endonuclease domain for cap-snatching (domain I or PA, segmented NS RNA viruses) or PRNTase/MTase domains for de novo cap synthesis (domains V and VI, nonsegmented NS RNA viruses). The regions containing cap formation enzymatic activities are also required for RNA synthesis, and the exact function of domains II and IV in the L protein of segmented NS RNA viruses remains unknown. EM of purified L from Machupo virus and vesicular stomatitis virus reveals a shared structural architecture conserved within NS RNA viral L proteins. L consists of a central ring-like RNA polymerase domain (blue highlight in cartoon) and a large appendage dedicated to 5' cap formation (maroon highlight in cartoon) attached with a flexible linkage. As described in the text, comparison with EM analysis and 3D reconstruction of the influenza virus polymerase complex provides further insight into the architecture of L. Influenza A virus polymerase images reproduced with permission from references 47 and 49.

Increased EM resolution and improved three-dimensional reconstructions will facilitate ongoing efforts to determine the high-resolution structure of L and individual enzymatic domains. Currently, the only high-resolution structures available are the L endonuclease domain from segmented viruses of the *Arenaviridae* and *Bunyaviridae* families[33,34] and the L ovarian-tumor protease domain unique to nairoviruses within the *Bunyaviridae* family.[54-56] Deletion mapping confirmed that the globular domains within

the VSV L appendage contain the PRNTase and MTase activities,[9] and by architectural comparison it is likewise predicted that the endonuclease structures relate to the end of the MACV L large arm-like domain.[8] However, exact placement of these structures will require considerably improved EM map resolution and additional future high-resolution structures.

Comparison of MACV and VSV L EM structures reveals a potential evolutionary path whereby an ancestral ring-like RNA-dependent RNA polymerase was appended with various cap formation activities to suit the specific requirements of different NS RNA viral replication mechanisms. Discrete domains dedicated to cap formation are further confirmed by the ability to express and independently fold a functional endonuclease domain from segmented L proteins[33,34] and the MTase domain from a nonsegmented L protein.[37] Similarly, it is possible to split the RNA-dependent RNA polymerase from the cap formation machinery and maintain an L protein capable of cellular-based replicon expression for both segmented L[52] and nonsegmented L proteins.[53] These genetic and biochemical experiments further support the EM maps of MACV and VSV L, and attest to the evolutionary addition of capping domains to a conserved RNA polymerase. Intriguingly, the L proteins of some segmented NS RNA viruses contain additional discrete domains dedicated to antagonism of the host antiviral machinery,[57-59] and indicate that the evolutionary process of domain addition is continually ongoing.

Regulation of L and Viral RNA Synthesis

Recombinant L has led to the reconstitution of RNA synthesis from purified components within both segmented and nonsegmented systems.[8,10-13] In combination with viral genetics and cellular-based RNA synthesis systems using genomic replicons, these in vitro assays allow the mechanistic study of template interactions and regulation of NS RNA viral gene expression. During infection, the genomic template for RNA synthesis is single-stranded RNA

tightly encapsidated within a protein sheath formed by the viral nucleocapsid (N) protein (reviewed in ref. 60). In spite of high-resolution structures, how L remodels this N-RNA template during mRNA transcription and genome replication remains a mystery. However, N is not required for RNA synthesis using short naked RNA templates in vitro[8,12,13] and is likely necessary for integrity of the full-length genome and reduction of RNA secondary structure.[60] Additionally, the N-encapsidated template is suggested to increase processivity of VSV L, indicating a further role for N in forming a fully elongation-competent polymerase complex.[13] The sequence and character of the RNA template itself also directs the viral polymerase machinery and can control L protein function. DsRNA intertermini interactions regulate the ability of arenavirus L to recognize a conserved 3'-CGUG-5' motif essential for polymerase recruitment and allows fine-tuning of viral gene expression.[8,61] Sequence-specific promoter interactions are also critical to activate cap-recognition and endonuclease activity within the influenza virus polymerase.[62,63] Although an exact sequence-specific recognition motif has not been identified for recruitment of nonsegmented viral L proteins, sequence-specific initiation events occur for VSV[13] and have been implicated with a variety of cellular-based replicon systems.

L from nonsegmented viruses is stimulated by the polymerase phosphoprotein cofactor (P).[64] No functional analog to P is required for segmented viruses, possibly due to differences in template interactions or primed[12,65,66] and de novo[13,67] RNA synthesis initiation. Additional viral cofactors have been implicated in modifying mRNA synthesis by nonsegmented NS RNA viral L proteins. The accessory proteins M2-1 of respiratory syncytial virus and VP30 of Ebola virus impact proper regulation of viral mRNA transcription,[68-70] but do not appear to be critical for genomic RNA replication. Studies with the influenza virus NS2 protein indicate that accessory factors may also control relative mRNA transcriptase and RNA replicase activities

of segmented NS RNA viruses.[71] In contrast to the core conserved enzymatic machinery, the divergent occurrence and function of accessory proteins reveals that regulation of NS RNA viral polymerase activity is complex and varies between viral systems.

In addition to accessory proteins, the major structural components of the virion have also been reported to serve regulatory roles influencing L for both segmented and nonsegmented viruses. This regulation has long been hypothesized to be important to ensure polymerase packaging into mature virions, and recent work has now revealed a possible mechanism for this connection.[12] All NS RNA viruses, dsRNA viruses and reverse-transcribing viruses initiate infection by first copying or transcribing the RNA genome inside an infected cell, and must therefore package their polymerase machinery in order to generate an infectious particle. Many viruses solve this problem by including the viral polymerase as an integral structural component of the virion, thereby rendering mature viral particle formation impossible in the absence of the polymerase. However, NS RNA viruses do not invoke this strategy, and it is possible to bud virus-like particles in the absence of the polymerase.[72-74] It has thus remained unclear how NS RNA viruses ensure the polymerase is packaged along with the N-RNA template during virion egress.

A possible safeguard to ensure accurate packaging of all necessary virion components resides within the diverse roles of the NS RNA viral matrix protein—the viral protein primarily responsible for mediating virion egress. In addition to recruitment of cellular machinery to promoter budding, overexpression of the matrix or matrix-like protein typically results in potent downregulation of viral gene expression in both segmented and nonsegmented systems (**Fig. 2**). Recently, the molecular basis for gene expression inhibition was determined for the arenavirus matrix protein (Z).[12] In addition to the known role in virion budding, Z was demonstrated to specifically interact with L and directly inhibit viral RNA synthesis independent of host cellular factors. Z-L complex

Figure 2. Inhibitory NS RNA viral proteins. Inhibition of gene expression by the viral matrix protein is a conserved feature of both segmented (top, orange) and nonsegmented (bottom, purple) NS RNA viruses. The Table indicates the NS RNA virus families and main individual viruses for which inhibition by matrix or other accessory factors has been observed.

	Family	Virus	Inhibitor	Gene	Reference
Segmented Genome	Arenaviridae	**Machupo virus**, lymphocytic choriomeningitis virus, Tacaribe virus, Lassa virus, Junín virus	Matrix	(Z)	12, 80, 92-94
	Bunyaviridae	Bunyamwera virus, Guaroa virus, Lumbo virus	Other?	(NSs)	78
	Orthomyxoviridae	influenza A virus	Matrix	(M1)	95, 96
Nonsegmented Genome	Bornaviridae	Borna disease virus	Other?	(X)	79
	Filoviridae	Ebola virus, Marburg virus	Matrix	(VP40, VP24)	77, 97
	Rhabdoviridae	**vesicular stomatitis virus**, rabies virus	Matrix	(M)	75, 98, 99
	Paramyxoviridae	Sendai virus, measles virus, respiratory syncytial virus, Nipah virus	Matrix + Other?	(M) (C/V)	100-105

formation catalytically inactivates L polymerase activity but does not impact promoter engagement, resulting in a frozen Z-L-RNA complex trapped on the 3' RNA promoter sequence. It is therefore hypothesized that this trapped complex not only regulates viral gene expression, but also serves as an intermediate to ensure a functional polymerase remains locked on the template and is packaged into mature virions. The intravirion concentration of the arenavirus matrix protein is sufficient to maintain L in a quiescent state within the viral particle, and once released into a newly infected cell the reduced local concentration of matrix will liberate the complex and free the polymerase to initiate a new round of infection (**Fig. 3**).[12]

Inhibition by overexpression of the viral matrix protein is a highly conserved feature of NS RNA viral replication (**Fig. 2**), and it is possible that arenavirus Z-L-RNA complex formation serves as an important paradigm for the link between transcription regulation and polymerase packaging of NS RNA viruses. In further support of this hypothesis, previous results with nonsegmented NS RNA viruses have demonstrated that matrix inhibits purified ribonucleoprotein complexes[75] and this inhibitory activity can be genetically separated from other functions of matrix during virion assembly.[76,77] Moreover, the two families of viruses that do not express inhibitory matrix proteins (segmented viruses of the *Bunyaviridae* family and

nonsegmented viruses of the *Bornaviridae* family), each encode alternative accessory proteins that downregulate polymerase activity and could maintain the conserved functional link between polymerase regulation and virion maturation (**Fig. 2**).[78,79]

If matrix has a conserved role in polymerase packaging, a key remaining question is how are levels of inhibitory matrix protein controlled such that they remain low enough to permit viral RNA synthesis and gene expression early during infection yet peak late when virion egress is favored over RNA production? Levels of Z vary throughout the arenavirus infection cycle,[80] and differential promoter strength and transcription from distinct genomic segments and individual

promoters can explain altered levels of inhibitory products for bunyaviruses and influenza A virus. However, the linear transcription mechanism of monopartite nonsegmented NS RNA viral genomes results in significant quantities of matrix produced throughout the entire replication cycle (reviewed in ref. 81). Interestingly, phosphorylation of matrix has been observed for representative members of all nonsegmented NS RNA viral families encoding an inhibitory matrix protein,[82-86] and hyperphosphorylation of matrix has been associated with inhibition of VSV RNA synthesis,[87] indicating alternative mechanisms such as control of a post-translational switch could determine when nonsegmented L proteins become template-locked and virion egress is favored.
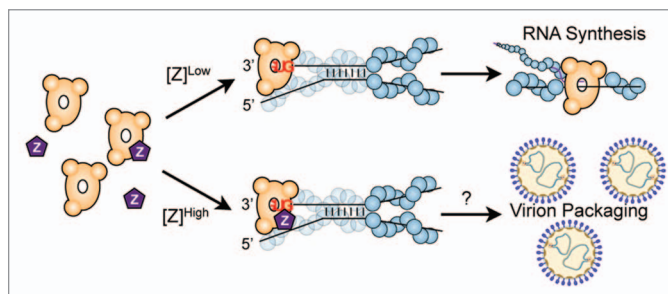

Figure 3. Model of arenavirus RNA synthesis regulation by the viral matrix protein. Low concentrations of matrix (Z) permit ongoing RNA synthesis, while high concentrations of Z result in an inhibited Z-L-RNA complex bound to the viral promoter. As described in the text, the Z-L-RNA complex may serve as an important intermediate ensuring L is packaged into mature virions. Other NS RNA viral matrix proteins or accessory inhibitory factors may play a similar role in viral replication, indicating a potentially conserved link between regulation of viral transcription and virion formation (figure adapted with permission from ref. 12).

However, successful rearrangement of gene order[88] and segment number[89] indicate the exact mechanisms regulating polymerase inhibitory proteins are likely more complex, and understanding the individual mechanisms at play for each virus will require significant future research. Reconstituted RNA synthesis systems available for influenza A virus and nonsegmented NS RNA viruses can now be used to directly assess polymerase inhibition by recombinant matrix protein and determine if the arenavirus packaging mechanism extends to other NS RNA viruses.

Perspectives

The future of NS RNA polymerase biology is inexorably tied to a further structural understanding of L and various cognate protein and N-RNA complexes. Low-resolution EM provides a tantalizing first glimpse of the basic machine,[8,9] but high-resolution studies are essential to decipher the working components of NS RNA replication. Continued development of in vitro systems should focus on reconstitution of template encapsidation for authentic viral replication studies and single-particle measurements capable of analyzing transition states and replication intermediates. Recently developed minimal RNA synthesis assays using naked RNA template hold great promise for high-throughput screening and discovery of small molecule inhibitors.[12,13] Nucleoside analogs like ribavirin and T-705[90] demonstrate the potential of broad-spectrum NS RNA polymerase antagonists, but many more steps of the replication cycle should also be prone to inhibition by small molecules.[91] Critically, as experiments become increasingly sophisticated and specialized to individual NS RNA viral systems, the instructive value of comparisons between segmented and nonsegmented viruses must not be overlooked.

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