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EXPRESSION OF THE REPLICASE TRANSCRIPTASE COMPLEX

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Abstract
The replicase–transcriptase complex (RTC) is a key component of the coronavirus replication cycle, responsible for viral genome replication and subgenomic RNA synthesis. Following the release of the viral nucleocapsid into the host cell cytoplasm, the replicase gene encoded within the viral genomic RNA is translated. Coronavirus replicase expression involves a unique ribosomal frameshifting mechanism that allows the production of large polyproteins, which are subsequently processed into multiple nonstructural proteins (nsps). These proteins assemble into the RTC and perform essential enzymatic and regulatory functions required for viral replication, transcription, and immune evasion. This article discusses the molecular mechanisms underlying RTC expression, the functions of major nonstructural proteins, and their significance in coronavirus biology and pathogenesis.

Keywords: Coronavirus, replicase–transcriptase complex, ribosomal frameshifting, nonstructural proteins, RNA-dependent RNA polymerase, viral replication, protease, helicase, RNA synthesis, immune evasion.

Introduction

Following the entry of the viral nucleocapsid into the cytoplasm, the next crucial event is the translation of the replicase gene from the genomic RNA. In coronaviruses, the replicase gene consists of two partially overlapping open reading frames (ORFs), namely rep1a and rep1b.

The synthesis of the complete replicase protein depends on a mechanism known as ribosomal frameshifting. During this process, the ribosome shifts one nucleotide backward with a certain probability, moving from the rep1a reading

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frame into the rep1b reading frame. This mechanism is regulated by two important RNA elements. The first is a conserved "slippery" nucleotide sequence found in all known coronaviruses, while the second is a complex RNA structure called a pseudoknot.

In most translation events, the ribosome proceeds to the stop codon of the rep1a gene, producing the shorter pp1a polyprotein. In some cases, however, the pseudoknot temporarily stalls ribosomal movement, causing a shift in the reading frame and allowing translation of the rep1b region. As a result, the larger pp1ab polyprotein is synthesized.

The pp1a and pp1ab polyproteins are subsequently cleaved through their own proteolytic activities into multiple mature proteins known as nsp1–nsp16 (nonstructural proteins). These proteins generate the enzymes and accessory factors required for viral replication.

Two types of proteases participate in polyprotein processing. The first group includes the papain-like proteases (PLpro), which cleave nsp1, nsp2, and nsp3. The second group consists of the main protease (Mpro or 3CLpro), which catalyzes the remaining cleavage events. Because these enzymes are essential for viral replication, they represent major targets for antiviral drug development.

Following proteolytic processing, the nonstructural proteins assemble to form the replicase–transcriptase complex (RTC). This complex controls viral genome replication and the synthesis of subgenomic RNAs.

Within the RTC, nsp1 suppresses host protein synthesis and inhibits interferon signaling pathways, thereby facilitating viral evasion of the host immune response. The function of nsp2 remains incompletely understood. nsp3, the largest RTC protein, contains multiple functional domains and exhibits both protease and deubiquitinase activities, contributing to the suppression of innate immune responses.

The proteins nsp3, nsp4, and nsp6 are associated with cellular membranes and induce the formation of specialized membrane structures required for viral RNA synthesis. During coronavirus infection, extensive membrane rearrangements occur, including the formation of double-membrane vesicles (DMVs) connected to the endoplasmic reticulum. These structures provide a protected

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microenvironment for viral RNA replication and shield viral RNA from host defense mechanisms.

Within the RTC, nsp7 and nsp8 form a large protein complex involved in RNA synthesis. nsp9 functions as a single-stranded RNA-binding protein, whereas nsp10 acts as a cofactor regulating the activity of several viral enzymes.

nsp12 contains the viral RNA-dependent RNA polymerase (RdRp), the central enzyme responsible for replication of the coronavirus genome. nsp13 functions as a helicase that unwinds double-stranded RNA structures and prepares the template for replication.

Several enzymes also participate in the formation of the 5′ cap structure of viral mRNA. nsp14 possesses N7-methyltransferase activity, while nsp16 functions as a 2′-O-methyltransferase. These enzymes modify viral RNA to resemble host cellular mRNA, thereby helping the virus evade immune recognition.

Coronaviruses possess two additional unique enzymes. The first is nsp15 endoribonuclease (NendoU), which participates in RNA processing and degradation. The second is nsp14 exonuclease (ExoN), which performs proofreading functions by correcting errors introduced during RNA replication. This proofreading activity is one of the main reasons why coronaviruses possess significantly larger genomes than most other RNA viruses.

Overall, the replicase–transcriptase complex represents the central molecular machinery of the coronavirus life cycle, coordinating genome replication, subgenomic RNA synthesis, immune evasion, and efficient viral propagation within host cells.

In addition to its core enzymatic functions, the RTC also plays a critical role in modulating host cell signaling pathways. Several nonstructural proteins, particularly nsp1, nsp3, and nsp6, actively interfere with innate immune sensing mechanisms. These interactions suppress the production of type I interferons and downstream antiviral responses, allowing the virus to establish a productive infection before strong immune activation occurs.

Another important aspect of RTC function is its ability to spatially organize viral replication within specialized intracellular compartments. The formation of double-membrane vesicles (DMVs) and associated membrane networks not only concentrates viral enzymes and RNA templates but also isolates replication

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intermediates from cytosolic nucleases and pattern recognition receptors. This compartmentalization is considered a key evolutionary advantage of coronaviruses.

Furthermore, the RTC exhibits a dynamic assembly process in which its components continuously interact and reorganize during different stages of infection. Early in infection, RTC formation is primarily driven by nsp3, nsp4, and nsp6-mediated membrane remodeling, whereas later stages involve increased recruitment of RdRp (nsp12) and its cofactors (nsp7 and nsp8) to sustain high levels of RNA synthesis.

Recent studies also suggest that RTC activity is tightly linked to host cell metabolism. Viral replication induces metabolic reprogramming, including enhanced lipid biosynthesis and altered energy utilization, which supports the formation and maintenance of replication organelles. This metabolic dependency highlights potential antiviral targets that extend beyond viral proteins to host factors.

Overall, the replicase–transcriptase complex functions not only as a replication machinery but also as a multifunctional regulatory system that coordinates viral RNA synthesis, immune evasion, and host cell remodeling, ensuring efficient viral propagation and persistence.

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