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Cytoplasmic ribonucleoprotein complexes, RNA helicases and coronavirus infection

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RNA metabolism in the eukaryotic cell includes the formation of ribonucleoprotein complexes (RNPs) that, depending on their protein components, have a different function. Cytoplasmic RNPs, such as stress granules (SGs) or P-bodies (PBs) are quite relevant during infections modulating viral and cellular RNA expression and as key players in the host cell antiviral response. RNA helicases are abundant components of RNPs and could have a significant effect on viral infection. This review focuses in the role that RNPs and RNA helicases have during coronavirus (CoVs) infection. CoVs are emerging highly pathogenic viruses with a large single-stranded RNA genome. During CoV infection, a complex network of RNA-protein interactions in different RNP structures is established. In general, RNA helicases and RNPs have an antiviral function, but there is limited knowledge on whether the viral protein interactions with cell components are mediators of this antiviral effect or are part of the CoV antiviral counteraction mechanism. Additional data is needed to elucidate the role of these RNA-protein interactions during CoV infection and their potential contribution to viral replication or pathogenesis.

KEYWORDS

coronavirus, stress granules, P-bodies, RNA helicase, MOV10, virus-host interaction

1 Introduction

Eukaryotic cell RNA is associated with proteins, forming ribonucleoprotein complexes (RNPs). The subcellular location of mRNAs in RNPs is a powerful mechanism for the spatial and temporal regulation of RNA processing events in the cell (1). In addition, by sharing components, different RNPs form a large regulatory network in cells.

The cytoplasm contains a number of RNPs that include specific mRNAs at various stages of post-transcriptional processing, including stress granules (SGs), processing bodies (PBs), neuronal bodies and exosome bodies (2). SGs and PBs are the most studied ones. Neuronal bodies are associated with the transport of translationally arrested mRNAs along the axon to dendrites (3, 4). Exosome bodies were proposed as sites for AU-rich element mediated mRNA decay containing exosome subunits (5). In the nucleus, the most studied RNPs are the Cajal bodies (CBs) (6), although the nucleus contains other RNPs such as nucleolus, nuclear speckles, nuclear stress bodies, histone locus bodies, paraspeckles and promyelocytic leukemia (PML) bodies (7–11). In general, these nuclear RNPs are sites of defined biochemical reactions, by concentrating reaction components in a confined space, and of gene activation or repression (12).

RNA helicases belong to an abundant protein family that is conserved from bacteria to humans, and are associated with all cellular processes involving RNA (13–16). RNA helicases are abundant components of cellular RNPs (17, 18). For instance, during gene expression, RNA helicases catalyze RNPs rearrangements starting with gene transcription and continuing with consecutive post-transcriptional steps, such as pre-mRNA splicing, mRNA export, translation and turnover (19–21).

Both cytoplasmic and nuclear RNPs have been involved in several disease conditions, including viral infections. This review is focused in the interplay between cytoplasmic RNPs, RNA helicases, and coronavirus (CoV) infections.

2 Cytoplasmic ribonucleoprotein structures

2.1 Classification and function

The most studied cytoplasmic RNPs are SGs and PBs. These structures are highly dynamic centers of mRNA sorting, storage and degradation, where the processes of splicing, non-sense mediated RNA decay (NMD), translation, turnover and RNA silencing intersect (Figure 1) (22–27). SGs are transient foci enriched in translation initiation factors and 40S ribosomal subunits, while PBs are enriched for RNA decay machinery. SGs and PBs each contain unique marker proteins although many proteins can be found in both SGs and PBs, such as eukaryotic translation initiation factor 4E (eIF4E), AU-rich RNA binding protein tristetraprolin (TTP), argonaute RISC catalytic component 2 (AGO2), apolipoprotein B mRNA-editing complex 3 (APOBEC3), poly(rC) binding protein 2 (PCBP2) and others (23, 28, 29). In fact, apart from having shared protein components, PBs and SGs dynamically exchange RNP cargo, often form co-aggregates and have been proposed to serve as nucleation sites for SGs formation (30, 31). SGs, PBs and other cytoplasmic foci are highly dynamic structures, although PBs are quite stable over the time (32). They are in a dynamic steady state with other RNPs, such as polysomes, in response to the translational state of the cell (23) (Figure 1).

SGs are 200-400 nm dynamic structures quickly formed when cells encounter external stresses and translation rates

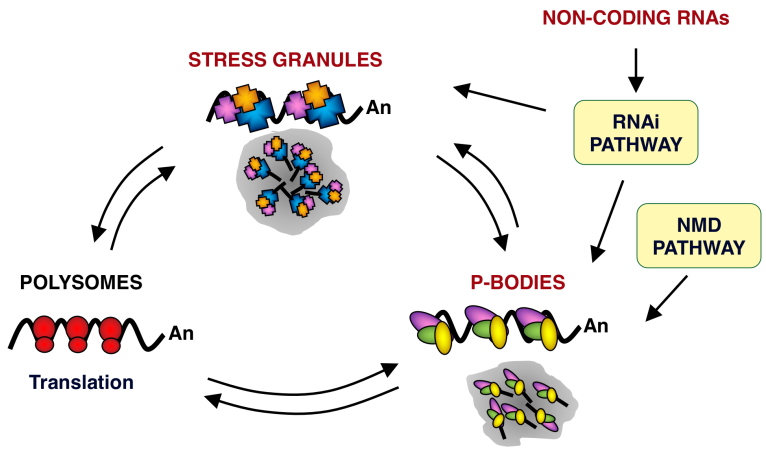

FIGURE 1
mRNA metabolism in eukaryotic cells. Schematic representation of mRNA locations in cells. mRNAs are found in three major RNPs: polysomes, PBs and SGs. PBs and SGs are large dynamic centers of mRNA sorting, storage and degradation. RNPs from and to polysomes and from and to SGs and PBs are in a dynamic equilibrium. Within PBs, RNPs could undergo further remodeling and define a path to follow, including their return to polysomes. In addition, PBs have been shown to interact and exchange components with SGs. PBs are also related to mRNA quality control mechanisms, such as NMD pathway. In silencing, non-coding RNAs function as the guide molecules that are incorporated into RNA-induced silencing complex (RISC) to control the translation and degradation of their target mRNAs within PBs and SGs. Arrows indicate the different equilibrium between RNPs. Ribosomes (red ovals), SG protein components (blue, orange and purple polygons) and PB protein components (yellow, green and purple ovals) are also represented.

decline, and disperse when translation conditions are restored (33, 34). The most commonly described triggers of SG formation are oxidative, starvation, heat stresses and infection with different pathogens. These stimuli activate eukaryotic translation initiation factor 2 alpha (eIF2α) kinases: heme-regulated kinase (HRI), general control non-depressible 2 kinase, (GCN2), dsRNA-activated protein kinase R (PKR) and PKR-like endoplasmic reticulum kinase (PERK). The eIF2α phosphorylation blocks translation, forcing an accumulation of the stalled 43S and 48S ribosomal preinitiation complexes. Inhibition of the function of eukaryotic translation initiation factors eIF4G or eIF4A (DDX2A) is also linked to SG formation (35) and some mechanisms of SG formation can proceed in the absence of eIF2α phosphorylation (36–38). The components of SGs can be classified into three main groups: core components, such as stalled initiation complexes; RNA-binding proteins associated to silencing and transcript stability, such as the scaffold proteins T-cell-restricted intracellular antigen 1 (TIA-1) or TIA-1-related protein (TIAR), and RNA-binding proteins associated to mRNA metabolism (23, 39–42). The key function of SGs is to protect the mRNAs during cell stress, altering the composition of the RNPs in a reversible manner (43). Moreover, SGs are generally believed to have an antiviral activity upon viral infection and many viruses manipulate SGs to evade host responses (2, 44–47).

PBs act as temporary reservoirs for non-translated mRNAs which may further enter translation or be degraded. PBs contain components of the 5' to 3' decay machinery, NMD pathway and RNA-induced silencing machinery (48). This enrichment on mRNA decay machinery components led to propose that significant RNA decay occurs within PBs. However, this is controversial since some activators of mRNA decay pathways found in PBs are translational regulators also present in SGs (29, 49). PBs are constitutively present in the eukaryotic cells but increase in size and number when translational arrest occurs, coincident with SG formation, resulting in physical interactions among SG and PB structures (23, 30). It has been described that mRNA degradation occurs in PBs and depends on the existence of degradation enzymes and mRNA degradation intermediates (50, 51). Many of the PB components are not restricted to these foci and are also present in the soluble cytoplasm and nucleus, suggesting that the different processes might start before the mRNAs entry into PBs.

2.2 Role of cytoplasmic RNPs in viral infections

Virus infection activates cell stress responses at many levels that modulate RNA granules. In general, RNP granules can represent an obstacle for virus replication and also serve as sensors to mount the innate immune response. Therefore, viruses have evolved different mechanisms to control the assembly and functions of RNP granules and, in some cases the components of RNPs are co-opted into novel virus-specific structures required for virus replication (52).

Mammalian orthoreovirus (MRV), a dsRNA virus, induces SGs at an early stage of the infection, correlating with reduced translation of both cellular and viral mRNAs and increased phosphorylation of eIF2α (53). Poliovirus inhibits SGs assembly at the late stages of infection, by a mechanism involving cleavage of SG protein Ras GTPase-activating protein-binding protein 1 (G3BP1), which is mediated by the viral 3C protease (54). In addition, TIA-1-containing granules persisted even at late stage of poliovirus infection, but those RNPs are remnants of normal SGs that do not correlate with translational repression (55, 56). Unlike MRV and poliovirus, Influenza A virus (IAV) prevents SG formation at all stages of the infection, by a mechanism depending on NS1 protein expression, since SGs inhibit IAV replication (57).

As an example of viral co-opting of RNP components, RNAs from flaviviruses, such as West Nile virus and Dengue virus, bind TIA-1 and sequester many PB components near or within perinuclear viral replication centers while the number of PBs was decreased (58). Human immunodeficiency virus (HIV)-1 TAT protein interacts with the PB component DDX3 to facilitate viral mRNA translation (59), and HIV-1 TAT protein is antagonized by antiviral factors APOBEC3 and Moloney leukemia virus 10 (MOV10), that are PB constituents (60–63).

CoVs are single-stranded RNA viruses with large genomes of around 30 Kb, which life cycle occurs in the cytoplasm of the infected cell. CoV RNA synthesis, including replication and transcription, is a complex process involving host cell membrane rearrangements, viral and cellular proteins (64, 65). Regarding the role of cytoplasmic RNPs in CoV infection, it has been shown that mouse hepatitis virus (MHV) replication induces host translational shutoff and mRNA decay, with concomitant formation of SGs and PBs (66). Porcine transmissible gastroenteritis virus (TGEV) triggers SG formation and interferes with PB formation, correlating with viral replication and transcription (67). Severe and acute respiratory syndrome (SARS)-CoV, SARS-CoV-2 and avian infectious bronchitis virus (IBV) nucleocapsid (N) proteins have been found to interact with the SG component G3BP1, and this has been proposed as a mechanism to avoid SG formation (68–72). In addition, porcine epidemic diarrhea virus (PEDV) promotes G3BP1 cleavage by caspase-8 (73) and Middle East respiratory syndrome (MERS)-CoV 4a accessory protein interferes with SG formation by inhibiting the activation of PKR binding to dsRNA, thereby inhibiting the formation of

SGs and ensuring viral protein translation and efficient virus replication (74, 75). It has been recently reported that SARS-CoV-2, HCoV-229E and HCoV-OC43 cause PB disassembly. In the case of SARS-CoV-2, this process may be mediated by N protein (76).

3 RNA helicases

3.1 Classification and function

RNA helicases share conserved helicase domains, all containing ATP binding motifs, providing the basis for helicases classification (Figure 2). Most cellular RNA helicases belong to the SF2 superfamily and only a few of them, the up-frameshift suppressor 1(Upf1)-like helicases (i.e., UPF1, also known as RENT1, and MOV10 helicase), belong to SF1. In contrast, many viral RNA helicases, such as CoV nsp13, belong to SF1 superfamily (77). The SF1 and SF2 helicases contain seven to nine conserved motifs that constitute the helicase core. In addition, SF2 RNA helicases, generally referred to as DExD/H box RNA helicases, are divided in five different subgroups (Figure 2): DEAD box (for the conserved amino acid residues Asp-Glu-Ala-Asp), DEAH (for the conserved amino acid residues Asp-Glu-Ala-His)/RHA, Ski2 (Superkiller-like 2)-like, retinoic acid-inducible gene I (RIG-I)-like, and Viral DExH proteins, named after one of the consensus amino acid sequence motifs (16, 78–80). The DEAD box (DDX) helicases are the largest subgroup within SF2, most of them involved in RNA metabolism, from transcription to degradation and in establishment of larger RNA-protein complexes, such as ribosomes (81, 82).

3.2 Role of RNA helicases in CoVs infection

Cellular DDX RNA helicases play essential roles in a broad array of biological processes and serve multiple roles at the virus-host interface (83–86). Specifically, DDX RNA helicases are hijacked by CoVs and participate in essential DDX-mediated viral replication steps (87). During CoV infection, these RNA helicases interact with viral proteins, as described below (Table 1). In addition, many of them interact with viral RNA (88–90) (Table 1), raising the possibility that these RNA helicase-CoV protein interactions are mediated by RNA.

DDX1, interacts with the nsp14 protein both from SARS-CoV and IBV, suggesting that this interaction may be conserved for other CoVs. DDX1-nsp14 interaction contributes to efficient CoV RNA replication in cell cultures (91). DDX1 also interacts with the nsp14 protein from TGEV, inducing interferon (IFN) production (92) and suggesting that nsp14 would be the viral component sensed by DDX1-DDX21-DHX36 cytoplasmic sensor, described in dendritic cells (93). Supporting CoV interaction with the DDX1-DDX21-DHX36 complex, N proteins of SARS-CoV-2 and IBV interact with DDX21, although the consequences of this interaction are still unclear (71, 94). In addition, phosphorylation of MHV N protein allows the recruitment of DDX1 to the CoV replication transcription complex (RTC), increasing the synthesis of longer viral RNAs, suggesting that this is one of the viral strategies to support the transition from discontinuous to continuous transcription (95).

The interaction between DDX3X and N proteins from SARS-CoV, SARS-CoV-2, or IBV was described (71, 96). Since

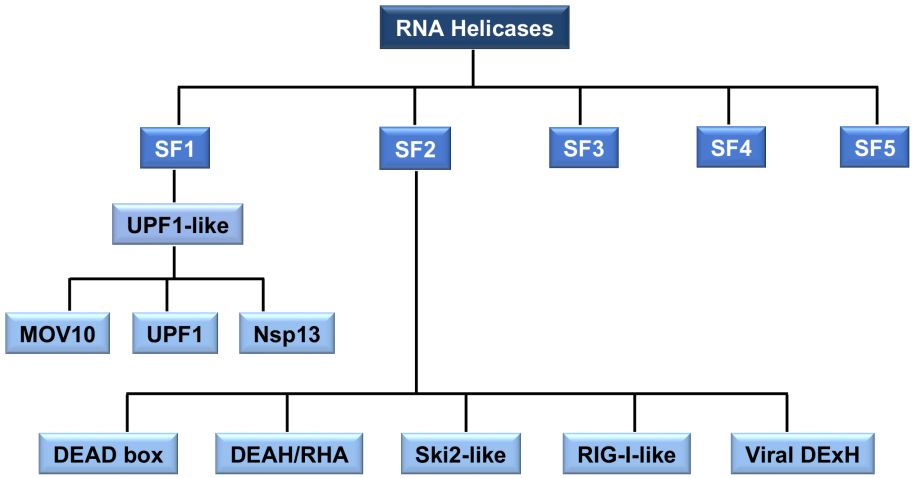

FIGURE 2
The classification of RNA helicases. All RNA helicases are classified into five superfamilies (SF) 1-5. SF1 and SF2 are sub-divided into distinct families and groups. SF1 is divided into Upf1-like family. SF2 is divided into five families. SF2 RNA helicase, DEAD box, DEAH/RHA, Ski2-like, RIG-I-like and Viral DExH, are collectively referred to as the DExD/H box of RNA helicases. The type of RNA helicases mentioned in this review, such as MOV10, UPF1, CoV helicase (nsp13), DEAD box and DEAH-box is indicated.

TABLE 1 RNA helicases involved in CoV infection.

HELICASE [a]	RNPs [b]	CoV	INTERACTING WITH [c]	ROLE
DDX1	SGs	IBV, MHV, SARS-CoV, TGEV	Nsp14, N, RNA	Proviral Antiviral. Part of dsRNA sensor DDX1-DDX21-DHX36
DDX3X (DDX3)	SGs, PBs	IBV, SARS-CoV, SARS-CoV-2	N, RNA	Antiviral
DDX5		SARS-CoV	Nsp13, RNA	Proviral
DDX6	SGs, PBs	HCoV-229E, HCoV-OC43, PEDV, SARS-CoV-2	RNA	Antiviral
DDX21	SGs	IBV, SARS-CoV-2	N	Unknown
DHX16		SARS-CoV-2	RNA	Antiviral. RNA sensor
DHX9 (DDX9)	SGs	SARS-CoV-2	n.d.	Unknown
MOV10	SGs, PBs	HCoV-229E, MERS-CoV, SARS-CoV, SARS-CoV-2, TGEV	N, RNA	Antiviral
UPF1	PBs	MHV, SARS-CoV-2	RNA	Antiviral

(a) Alternative names in brackets, in agreement with the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC, https://www.genenames.org).
(b) RNPs, Cytoplasmic ribonucleoprotein complexes.
(c) CoV components. Nsp, non-structural protein; N, nucleocapsid protein; n.d., non-determined.

DDX3X is involved in the activation of the innate immune response at different levels (97–99), it was suggested that N protein can modulate the immune response by binding to DDX3X and inhibiting these antiviral pathways, as demonstrated for other viruses (100). SARS-CoV nsp13 interacts with DDX5 and inhibition of DDX5 results in the suppression of viral replication. A proviral function for DDX5 has been suggested, maybe acting as nsp13 co-activator during RNA synthesis (101). In addition, since DDX5 is involved in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) response, the binding between nsp13 and DDX5 can also have the role of evading host inflammatory response (102). Interestingly, DDX5 interacts with other DEAD box helicases, such as DDX3X and its close homolog DDX17. The phosphorylation-dependent interaction between DDX5 and DDX3X was proposed as a combined mechanism of action for DEAD box helicases involved in RNP remodeling and splicing, by forming a complex that functions in shuttling RNP export from the nucleus to the cytoplasm (103, 104).

DDX6, a helicase located in SGs and PBs, is downregulated during PEDV infection to reduce endoplasmic reticulum (ER) stress, facilitating viral replication (105). The accumulation of DDX6 is decreased by HCoV-OC43 infection, while it does not change with HCoV-229E or SARS-CoV-2 infection (76). DDX6 interacts with RIG-I to increase antiviral signaling and IFN induction (106). However, the potential effect of DDX6 innate immunity modulation during PEDV infection was not analyzed as IFN incompetent Vero cells were used.

There is also recent evidence of other RNA helicases being involved in the immune response during SARS-CoV-2 infection. DHX16 has been described as a novel sensor for SARS-CoV-2 replication, triggering IFN response (107). The levels of DHX9 expression in effector TCD8+ cells have been correlated with better COVID-19 outcome (108).

3.3 MOV10

MOV10 protein is a UPF1-like RNA helicase (109, 110). MOV10 helicase has more than 1060 interactors, according to BioGRID database (111), some of them linking MOV10 to RNA metabolism pathways such as the NMD pathway or the siRNA gene silencing pathway. In fact, depletion of MOV10 mRNA by using siRNAs interferes with RNAi activity (110, 112). In addition, MOV10 is an IFN-stimulated gene (ISG) (113) and MOV10 protein is involved in IFN induction after viral infection (114).

Both proviral and antiviral functions have been reported for MOV10. As a proviral factor, it is required for hepatitis delta virus (HDV) replication but not for the translation of its mRNA (115) and facilitates enterovirus replication (116). As an antiviral factor it inhibits: (i) HIV-1 and other retroviruses replication at multiple steps (63), (ii) nuclear import of influenza virus nucleoprotein (117), (iii) porcine reproductive and respiratory syndrome virus (PRRSV) replication by avoiding nucleocapsid protein trafficking to the nucleus (118), (iv) hepatitis C virus (HCV) and Dengue virus replication by a partly unknown mechanisms (119, 120), and (v) bunyavirus replication by blocking several nucleoprotein functions (121). In the case of hepatitis B virus (HBV), contradictory data has been reported for both, its proviral (122) and antiviral activities (123).

The role of MOV10 during CoV replication has recently been analyzed by our group. The interaction between endogenous MOV10 and N protein during infection was

demonstrated for porcine TGEV virus, and both mild (HCoV-229E) and highly pathogenic CoVs (SARS-CoV, MERS-CoV and SARS-CoV-2) (124). This interaction was also reported by other authors, outside the infection context using N protein overexpression (71, 94, 125). During MERS-CoV infection, both MOV10 and N protein co-localized in cytoplasmic RNPs, not related with CoV RTCs, that may eventually contain also other cellular proteins, such as TIAR, AGO2 or UPF1 (124) (Figure 3). Functional analyses indicated that MOV10 has antiviral activity during MERS-CoV and SARS-CoV-2 infection, but not during HCoV-229E infection, suggesting a relationship with CoV pathogenesis that will be further explored (124). In agreement with other previously described MOV10 interactions with cellular proteins, MOV10 interaction with CoV N protein was RNA-dependent (124). Interestingly, MOV10 interaction with SARS-CoV-2 RNA was recently described (88, 90, 126–128) and it was conserved for other human CoVs (127). This issue opens the possibility of N protein having an active role in the MOV10 antiviral activity or of its non-specific recruitment to MOV10 RNPs, mediated by its binding to viral RNAs. In contrast with other viral infections, MOV10 helicase activity was required for antiviral function during MERS-CoV infection (124). The binding of MOV10 and CoV N protein was conserved independently of MOV10 antiviral activity, i.e., with a MOV10 mutant without helicase activity, or in HCoV-229E infection (124), suggesting that N binding to MOV10 is not related with MOV10 antiviral function. In addition, CoV N protein has been proposed to subvert SGs or counteract NMD pathway to facilitate viral replication (129, 130). Therefore, additional experimental evidence is needed to determine whether N protein may have an active role in the formation or function of MOV10 RNPs.

4 Conclusion and future perspectives

RNA-protein interactions leading to RNPs formation represent one of the mechanisms for post-transcriptional regulation of protein expression. Viruses interact with host cell RNPs to facilitate viral replication and to counteract antiviral responses. In the case of CoVs, cytoplasmic RNPs have, in general, an antiviral effect. Therefore, CoVs have developed mechanisms to antagonize RNPs formation or function.

The interaction between CoVs and cellular RNA helicases is a clear example of the complex network of interactions that may have different contributions to the outcome of the infection. Some RNA helicases, as DDX1, are recruited to CoVs RTCs to facilitate viral RNA synthesis, having a proviral function. On the other hand, RNA helicases have also an antiviral function mediated by their role in the innate immune response to the infection or by forming RNPs. These issues are frequently related, as RNPs components, both RNAs

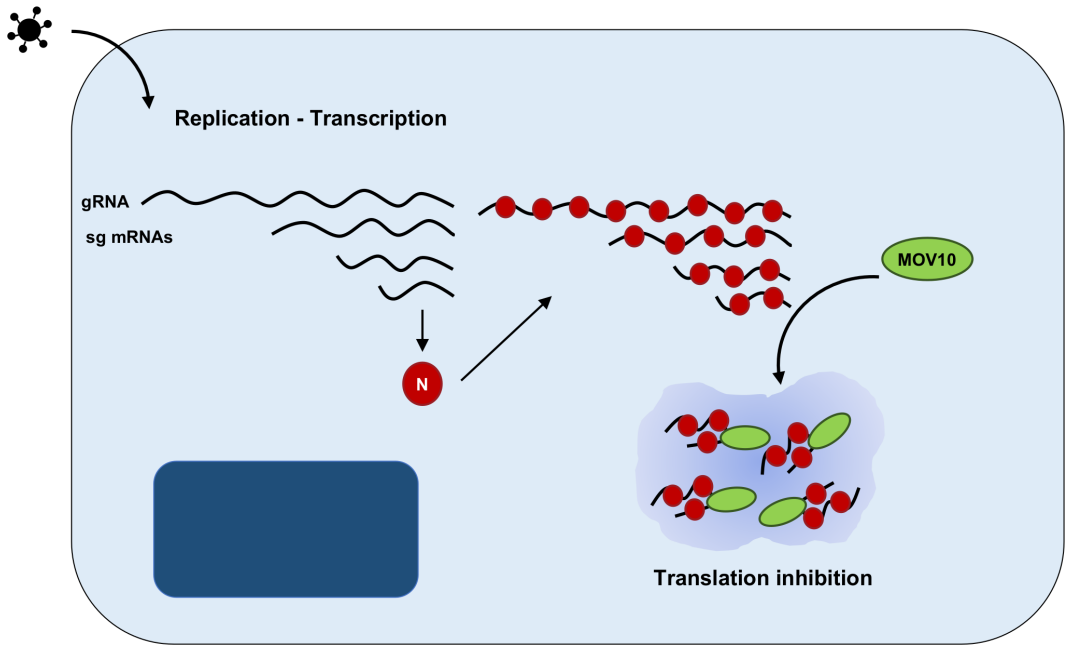

FIGURE 3
Proposed model of MOV10 antiviral function during MERS-CoV infection. Schematic representation of an infected cell, including nucleus (dark blue) and cytoplasm (light blue). CoV replication and transcription leads to the synthesis of a nested set of viral RNAs, both viral genome (gRNA) and subgenomic mRNAs (sgmRNAs). N protein is translated from the subgenomic RNA and binds to viral RNAs. The RNA-dependent interaction between N protein and MOV10 may lead to the accumulation of viral RNAs and N protein in cytoplasmic RNPs, inhibiting viral translation.

and proteins, may have a direct effect on the expression of innate immune factors.

There is limited knowledge on the interactions and functions of RNA helicases or RNPs in CoV infection, especially in the infection context. Recent omics approaches may help to decipher the composition and function of RNPs during CoV infection. However, some of the interactions occur between cellular proteins and essential viral factors, which cannot be modified to directly analyze the impact on infection. In addition, RNPs components often have a functional redundancy or are shared between different RNPs with different functions. Moreover, RNPs are dynamic and could be dependent on the cell type or infection stage. Therefore, it would be challenging to unravel these virus-host interaction networks and how they contribute to viral replication and pathogenesis.

Author contributions

LW, MG and SZ made the literature review, prepare the figures and tables, and wrote the manuscript. IS, SZ and LE assisted in the writing and revision of the manuscript. All authors contributed to the review article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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