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MINI-REVIEW

Selective regulation in ribosome biogenesis and protein production for efficient viral translation

Hui-Jun Dong[1] · Rui Zhang[1] · Yu Kuang[1] · Xiao-Jia Wang[1]

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Abstract

As intracellular parasites, viruses depend heavily on host cell structures and their functions to complete their life cycle and produce new viral particles. Viruses utilize or modulate cellular translational machinery to achieve efficient replication; the role of ribosome biogenesis and protein synthesis in viral replication particularly highlights the importance of the ribosome quantity and/or quality in controlling viral protein synthesis. Recently reported studies have demonstrated that ribosome biogenesis factors (RBFs) and ribosomal proteins (RPs) act as multifaceted regulators in selective translation of viral transcripts. Here we summarize the recent literature on RBFs and RPs and their association with subcellular redistribution, post-translational modification, enzyme catalysis, and direct interaction with viral proteins. The advances described in this literature establish a rationale for targeting ribosome production and function in the design of the next generation of antiviral agents.

Keywords Selective translation · Ribosome biogenesis factor · Ribosomal protein · Antiviral target

Introduction

Initiation, as the first stage of translation, can be carried out by either cap-dependent or cap-independent mechanism in eukaryotic cells (Kapp and Lorsch 2004). The majority of the eukaryotic genome is translated via cap-dependent translation initiation, mainly through the 43S preinitiation complex (PIC) binding to the mRNA 5′-end cap structure and scanning along the mRNA to the AUG initiation codon to initiate translation (Haimov et al. 2015). In contrast to the cap-dependent mechanism, the cap-independent mechanism is translated by 43S PIC (or a single 40S unit in some specific mRNA templates) directly binding to the internal ribosome entry site (IRESs) in the genome intergenic region (Kapp and Lorsch 2004). The number and types of translation initiation factors required for IRES-mediated translation initiation can vary significantly among specific mRNA species. For example, eIF4E is not required for IRES-mediated picornavirus genome translation (Avanzino et al. 2017), and IRES elements present in the hepatitis C virus (HCV) genome require fewer translation initiation factors to initiate translation (Torrecilla et al. 2016; Kerr et al. 2016).

Ribosomes are apparatuses that catalyze protein synthesis. The eukaryotic 80S ribosome is composed of two subunits: the 40S subunit contains the decoding center, which monitors the complementarity of transfer RNA (tRNA) and messenger RNAs (mRNA) and is composed of 33 ribosomal proteins (RPs), and the 60S subunit, which catalyzes the formation of peptide bonds and is composed of 47 RPs (Khatter et al. 2015; Barna 2013). Ribosome biogenesis is a complex process, which takes place mainly within the nucleoli of eukaryotes, and requires more than 300 ribosomal biogenesis factors (RBFs) (Tafforeau et al. 2013). RPs are coordinated with ribosomal RNA (rRNA) to synthesize, mature, assemble, and export into the cytoplasm, and they are crucial participants in the cellular process of translation from mRNA (Lafontaine and Tollervey 2001; Moore 2012).

Ribosome-mediated translational regulation can be explained by two different models (Shi et al. 2017; Simsek et al. 2017). The ribosome-concentration hypothesis

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✉ Rui Zhang
2015001@cau.edu.cn

✉ Yu Kuang
kuangyu@cau.edu.cn

✉ Xiao-Jia Wang
wangxj@cau.edu.cn

[1] Key Laboratory of Animal Epidemiology of the Ministry of Agriculture, College of Veterinary Medicine, China Agricultural University, Beijing 100193, China

proposes that the changes in cellular ribosome abundance may be a major driver of changes in translation of mRNA pools. The specialized ribosomes hypothesis is based on the finding that some RPs differ in composition and specifically regulate a subset of specific mRNA (such as RPL38 for Hox mRNA) translation (Shi and Barna, 2015; Xue and Barna, 2012; Simsek et al. 2017; Briggs et al. 2017; Genuth and Barna, 2018). RBFs control ribosome biogenesis to participate in the cellular process of mRNA translation. Several viruses have evolved sophisticated mechanisms that utilize cellular translational machinery to obtain efficient viral protein synthesis and viral replication (Hilton et al. 1986; Narayanan et al. 2008; Li et al. 2018a, b).

The ribosome itself (primarily ribosomal proteins), and the ribosomal biogenic processes that are exploited by viruses to facilitate their own replication, should be considered as targets in the development of antiviral agents, as depicted in Table 1 and as summarized in this study.

The roles of ribosome biogenesis in viral replication

Ribosome biogenesis is critical for cell proliferation and stress response. The synthesis of viral proteins depends on the host ribosome, and ribosome biogenesis has implications for viral infection through the effects of RBFs on viral transcription, proliferation, and antiviral immune responses, as well as the effects of viral proteins on ribosomal biosynthesis.

Regulation of RBFs in viral infection

Ribosomal RNA transcription, catalyzed by RNA polymerase I (Pol I), plays a critical role in ribosome biogenesis. Transcriptional activation of rRNA is also closely associated with viral infection. However, restricting ribosome biogenesis by interfering with rRNA accumulation-triggered ribosomal stress stimulated the viral replication of human cytomegalovirus (HCMV); the process inhibited the expression of innate immune-related genes, such as the high-mobility group Box 2 (HMGB2). This reveals that rRNA accumulation and/or ribosome biogenesis regulate innate immune responses to restrict virus reproduction and regulate inflammation (Bianco and Mohr 2019). Similarly, ribosomes are required for the protein synthesis of host cells and viruses, but the biogenesis factor RBFs can also impact the proliferation of virus and cell-intrinsic immune responses.

At this intersection of apparently competing processes, it is intriguing to find RBFs that are required specifically for the viral protein biosynthesis, but do not affect global translation. NOP53 (GLTSCR2/PICT-1), for example, shares homology with the yeast 60S ribosomal protein Nop53p, which acts as an essential ribosome biogenesis factor (Sydorskyy et al. 2005; Thomson et al. 2005). A previous study by the present author showed that NOP53, expressed as a set of discrete globular structures within the nucleolus, is migrated to the cytoplasm upon infection by herpes simplex virus 1 (HSV-1) (Meng et al. 2018). Furthermore, the cytoplasmic translocation of NOP53 is required for efficient viral replication, which occurs via depression of the activity of innate immune receptor RIG-I and decrease of the phosphorylation level of eIF2α to facilitate the production of viral proteins without affecting global protein synthesis (Meng et al. 2018, 2019). Similarly, both nucleolar proteins of ribosomal RNA processing 1 homolog B (RRP1B) and nucleolin are involved in ribosomal biogenesis (Chamousset et al. 2010). RRP1B associated with pre-60S ribosomal subunits was translocated to the nucleoplasm upon viral infection of influenza virus, where RRP1B improves viral RNA-dependent RNA polymerase (RdRp) activity, which is responsible for virus transcription and replication (Su et al. 2015). Nucleolin, which is thought to control RNA metabolism and ribosome biogenesis (Cong, et al. 2012; Allain 2000), is prevented from entering the nucleus in poliovirus-infected cells (Waggoner 1998); this allows stimulation of IRES-mediated translation of viral transcripts (Izumi 2001). Upstream binding factor (UBF) plays a major role in the regulation of rRNA synthesis and associates with viral replication of adenovirus; the antibody against UBF reduces viral replication (Lawrence et al. 2006).

In mammalian cells, there are two sets of ribosome particles, which reside in the cytoplasm and the mitochondria. Some viruses manipulate mitochondrial biogenesis to support replication. It has been reported that the protein levels involved in mitochondrial ribosome biogenesis are significantly up-regulated by infection with human cytomegalovirus (HCMV). The inhibition of mitochondrial translation with chloramphenicol or knockdown of ribosome biogenesis factor MRM3 abolished the HCMV-mediated increase in mitochondrial coding proteins and significantly impaired viral growth (Karniely et al., 2016).

Regulation of ribosome biogenesis in the nucleolus by viral proteins

The main function of the nucleolus is in ribosome biogenesis, regulation of the cell cycle, and the response to cellular stress. Many viral proteins, such as the nucleocapsid protein of coronavirus (Chen et al. 2002; Cawood et al. 2007; Dove et al. 2006; Emmott et al. 2010; Hiscox et al. 2001; You et al. 2005), the matrix protein of Newcastle disease virus (NDV) (Peeples et al. 1992), and the non-structural protein 1 of influenza virus (Melén et al. 2002), transport to the nucleolus to regulate ribosome biosynthesis, change the nucleolar morphology, or affect the function of the

Table 1 Ribosomal proteins and ribosome biogenesis factors utilized for viral infection

RPs/RBFs	Virus	Functions for viral infection	Reference
RPSA	FMDV	FMDV VP1 interacts with RPSA to promote viral replication	Zhu et al. 2019
RPS5	HCV	Interacts with the IRES of HCV for optional translation of viral transcripts	Fukushi et al. 2001; Bhat et al. 2015
RPS6	HCV	Acts as an indispensable host factor for HCV propagation	Huang et al. 2012
	KSHV	Interacts with the latency-associated nuclear antigen of KSHV	Chen et al. 2011
RPS9	HCV	Interacts with the IRES of HCV for optional translation of viral transcripts	Fukushi et al. 2001
RPS3	HIV-1	Interacts with viral Tat to inhibit cell proliferation	Kim and Kim 2018
RPS2	WNV, DENV, YFV	Acts as receptor interacting with viral envelope protein E	Zidane et al. 2012
RPS19	Hantavirus	Required for initiation of viral nucleocapsid protein-mediated translation	Cheng et al. 2011
RPS20	Poxvirus	Ubiquitination is specifically required for synthesis of viral proteins	DiGiuseppe et al. 2018
RPS25	CrPV, HCV, HTLV-1, Poliovirus, Adenovirus	Required for initiation of viral IRES-mediated translation	Landry et al. 2009; Hertz et al. 2013; Olivares et al. 2014
RPS27	IAV	Facilitates viral replication and infectivity	Karlas et al. 2010
RPS27a	EBV	Enhances viral proliferation and invasion by stabilizing LMP1	Hong et al. 2017
RACK1	HCV	Facilitates initiation of viral IRES-mediated translation	Majzoub et al. 2014; Ullah et al. 2019
RPL4	IBDV	Modulates viral replication as interaction partner of viral VP3 protein	Chen et al. 2016
	EBV	Acts as essential host factor for EBV Nuclear Antigen 1 function	Shen et al. 2016
RPL6	HTLV-1	Facilitates proliferation of HTLV-I	Wang et al. 2002
RPL7	HIV-1	Facilitates virus particle assembly as a Gag binding partner	Mekdad et al. 2016
	WSSV	Interacts with VP51 to participate in WSSV infection	Liu et al. 2015
RPL9	MMTV	Facilitates virus particle assembly as a Gag binding partner	Beyer et al. 2013
RPL18	RSV	Interacts with nucleocapsid protein to participate in RSV infection	Li et al. 2018a, b
RPL40	VSV, RABV	Promotes efficient translation of viral transcripts	Lee et al. 2015
RPLP1/P2	DENV, YFV,	Act as essential host factors for early viral protein accumulation	Campos et al. 2017
RPL10a	ZIKV HCV, CrPV	Regulate viral IRES-mediated translation	Shi et al. 2017
RPL13	FMDV	Interacts with viral IRES in helicase DDX3-dependent manner	Han et al. 2019
NOP53	HSV-1	Cytoplasmic translocation associated with efficient viral replication	Meng et al. 2018; 2019
RRP1B	IAV	Acts as essential host factors for IAV transcription	Su et al. 2015
Nucleolin	Poliovirus	Stimulates IRES-mediated translation of the poliovirus genome	Izumi et al. 2001
MRM3	HCMV	Essential host factor for mitochondrial coding proteins and viral replication	Karniely et al. 2016
UBF	Adenovirus	Associates with the replication of viral DNA	Lawrence et al. 2006
NPM	HBV	Interacts with HBx and mediates its oncogenic effects	Ahuja et al. 2015
DDX5	SARS-CoV, IBV, HIV-1, HCV	Recruited by viral proteins to facilitate viral replication	Chen et al. 2009; Zhou et al. 2013; Goh et al. 2004; Bortz et al. 2011

nucleolus. During nucleocytoplasmic shuttling, viral proteins can recruit nucleolar RBFs to modulate ribosomal biosynthesis for efficient viral replication. The multifunctional nucleolar phosphoprotein nucleophosmin (NPM) plays a lead role in ribosome biogenesis to stimulate RNA Pol I-dependent transcription (Li and Hann 2013) and regulates

the export of ribosomal proteins and mature ribosomes to the cytoplasm (Yu et al. 2006). The HBx oncoprotein of hepatitis B virus (HBV) directly interacted with the C-terminal domain of NPM to stimulate viral transcription (Ahuja et al. 2015). Several RNA helicases have been demonstrated to facilitate ribosome biogenesis, involving the processing of ribosomal RNA (rRNA) as well as its assembly into functional ribonucleoprotein complexes (Bleichert et al. 2007). DDX5 promotes the synthesis and maturation of rRNA and ultimately increases ribosome output and proliferation (Jalal et al. 2007). Many viral proteins, such as coronavirus nsp13 (Chen et al. 2009), Rev of human immunodeficiency virus 1 (HIV-1) (Zhou et al. 2013), NS5B of hepatitis C virus (HCV) (Goh et al. 2004), and NP protein of influenza virus (Bortz et al. 2011) have evolved to hijack DDX5 in order to facilitate viral replication. Studies on the regulation or manipulation of viral protein in ribosome biosynthesis provides new insights into efficient viral replication.

The roles for RPs in canonical translation and cap-independent translation

The ribosome was once considered to be a large protein synthesis machine that merely translated mRNAs into proteins. In recent years, however, the role of ribosomes in the regulation of initiation and selection of mRNAs has been the subject of increased attention. Most RPs are essential for translation and viral replication, and regulate translation of viral mRNAs as constituents of the ribosome, although a few represent the defense signaling of host cells (Zhou et al. 2015). (The role of RPs in activating an immune response is beyond the scope of the present paper.) Of particular interest are the RPs that are non-essential to the function of the ribosome, such as the large ribosomal subunit (RPL40, RPL38) and the small ribosomal subunit (RPS27, RPS25) (Jack et al. 2011; Karlas et al. 2010; Xue et al. 2015; Lee et al. 2013).

In the process of coevolution with hosts, viruses have evolved different strategies to inhibit host translation or induce host translation shutoff while protecting their own protein synthesis. Many viruses globally interfere with host translation by impairing cap-dependent ribosome recruitment to host mRNAs. For example, vesicular stomatitis virus (VSV) inhibits the translation of host mRNAs in infected cells, but allows the translation of its own capped mRNAs (Whitlow et al. 2008; Wertz and Youngner 1970). RPL40 promotes efficient translation of VSV mRNAs in a cap-dependent manner, but is not required for global protein synthesis (Lee et al. 2013). This may represent an endogenous specialized translation function for RPL40. Influenza A virus (IAV) viral mRNAs, on the other hand, are not preferentially translated compared to their host counterparts, and the extensive translation of viral proteins is the result of viral takeover of the mRNA pool in the cell (Bercovich-Kinori et al. 2016). Ribosome footprints and mRNA read density analysis reveal that RPs are not strongly affected by IAV infection but are enriched for genes involved in pathways that the virus may depend on (Bercovich-Kinori et al. 2016). Moreover, IAV encodes C4-type zinc finger peptide (ZFP) motif-containing viral protein (such as matrix protein M1) for replication and virus budding (Fernandez-Pol et al. 2001); RPS27 also contains a ZFP motif, and has recently been reported to facilitate translation and viral replication (Fernandez-Pol et al. 2001; Fernandez-Pol 2011). When RPS27 is eliminated, the replication and infectivity of IAV is abolished, but it is dispensable for global protein synthesis (Karlas et al. 2010). Research on the essential viral and cellular ZFP motif-containing proteins has implications for the prevention and therapy of viral diseases, and these proteins should be considered as targets for novel antiviral compounds.

In eukaryotes, certain RPs control selectivity during IRES-driven translation. For example, RPL38 and RPL35 control the selective translation of a specific mRNA by promoting translation primarily at the initiation stage (Kondrashov et al. 2011; Jiang et al. 2015; Xue et al. 2015). Several viruses whose genomes lack a 5′-end cap structure use cap-independent mechanisms for translation initiation (Daijogo and Semler 2011; Martinez-Salas et al. 2015). These viruses have in fact evolved to hijack specific RPs to achieve optimal viral protein synthesis; they facilitate translation of viral transcripts of IRES-containing viruses. The RPs include RPS25 (Landry et al. 2009), RPS5 (Fukushi et al. 2001; Bhat et al. 2015), RPS6 (Huang et al. 2012), RPS9 (Fukushi et al. 2001), and RACK1 (Majzoub et al. 2014), as well as RPL10a (Shi et al, 2017), RPL22 (Wood et al. 2001), and RPLp1/2 (Campos et al. 2017). Of these, RACK1 (Majzoub et al. 2014) and RPS6 (Huang et al. 2012) are specifically required for IRES activity in various types of viral IRESs. RPL10a regulates translation from the HCV and cricket paralysis virus (CrPV) IRESs but not from the encephalomyocarditis virus (EMCV) IRES (Shi et al, 2017). In other words, RPL10a is an example of an RP that plays a specific role in promoting translation of particular classes of viral IRESs. RPS25 is essential for initiation from the HCV and CrPV IRES (Landry et al. 2009). RPS25 deletion in yeast or mammalian cells has minimal effects on cellular protein synthesis, which implies that this ribosomal protein may be selectively required for viral IRES-mediated translation (Jack et al. 2011; Hertz et al. 2013). Similarly, RACK1 is not required for cellular IRESs or global synthesis (Majzoub et al. 2014). Overall, RPs specifically required for protein synthesis in particular viruses but not for global synthesis may provide an effective target for methods to fight viral infection.

Alterations in functional characteristics of RPs for viral translation

Some of the related functions of RPs are ribosome-dependent, as when RPs participate in viral protein biosynthesis, and other functions, typically involved in the regulation of infection in host cells, are independent of the ribosome. Alterations in RP characteristics for optional translation are implicated in interaction with viral proteins, post-translational modification, and redistribution, directly or with the assistance of RNA helicase.

RPs interact with viral proteins

Some viruses have developed to hijack specific RPs using viral proteins to achieve optimal viral translation. IBDV VP3 is a multifunctional protein playing a key role in virus assembly and pathogenesis. Ribosomal protein L4 (RPL4) (Chen et al. 2016) and ribosomal protein L18 (Wang et al. 2018) were identified as interacting partners of VP3 protein and as being involved in the regulation of IBDV replication. RPL18 interacts with nucleocapsid protein of rice stripe tenuivirus (RSV), and silencing RPL18 significantly reduces viral mRNA translation and replication of RSV (Li et al. 2018a, b). RPL7 interacts with the VP51 to participate in viral infection of white spot syndrome virus (WSSV), and the addition of anti-RPL7 antibody inhibits WSSV infection in *Litopenaeus vannamei* (Liu et al. 2015). Among flaviviruses, the envelope protein of West-Nile virus (WNV), dengue virus (DENV), and yellow fever virus (YFV) bind with RPSA, which serves as the viral receptor (Zidane et al. 2012). As regards alphaviruses, RPSA includes different binding sites for Venezualian equine encephalitis virus (VEEV) and Sindbis virus (SINV) (Jamieson et al. 2008; Malygin et al. 2009). HIV-1 Tat inhibits cell proliferation via an interaction with RPS3 and increases the level of RPS3 in the nucleus, thereby disrupting mitotic spindle formation during HIV-1 infection (Kim and Kim 2018). FMDV VP1 inhibits the antiviral response of RPSA by interacting with RPSA to promote FMDV replication (Zhu et al. 2019). Binding of viral proteins to specific RPs plays a crucial role in viral infection. Effective inhibition of the binding between RPs and viral proteins can be a potential target for antiviral design.

Post-translational modification of RPs

Post-translational modifications such as phosphorylation, ubiquitination, acetylation, methylation, or O-GlcNAcylation activate, deactivate, or modify RP's functions. Over 2,500 modifications of human RPs have been reported; these modifications impact RP activity and subsequently modify the global rate of translation by modulating initiation, elongation, and termination rates (Emmott et al. 2019). One well-studied modification on the ribosome is phosphorylation following activation or inhibition of intra and extracellular signaling cascades in response to stimuli occurring in physiological or pathological conditions (Emmott et al. 2019). Phosphorylation of RPS6 is perhaps the most widely studied ribosomal protein phosphorylation among the RPs involved in virus infection; it is induced by various viral infections (Kennedy et al. 1981; Kennedy and Leader 1981; Decker 1981; Banham et al. 1993; Beaud et al. 1994). In addition, an early study revealed that phosphorylation of RPL30 was induced by herpes simplex virus-1 (HSV-1) (Simonin et al. 1995). RPSa, RPS2 and RPS13 appear specifically phosphorylated in cells early after infection with vaccinia virus (Kaerlin and Horak 1978; Buendia et al. 1987). Efficient phosphorylation of the ribosomal proteins correlates well with possible translational mechanisms, ensuring efficient expression of early and late genes of vaccinia virus. It has been shown that phosphorylation of the RACK1A protein on two residues—Ser-122 and Thr162—by an atypical serine/threonine protein kinase WNK8 (With No Lysine8) negatively regulates RACK1A function in the glucose responsiveness pathway by influencing its protein stability (Urano et al. 2015). RACK1A proteins are phosphorylated by tyrosine, depending on diverse environmental stresses (Sabila et al. 2016). Viral infection leads to activation of ribosomal protein phosphorylation, which may be closely related to effective viral translation. The change of phospho-RP level may affect viral translation. However, despite reports on the increasing phosphorylation of RPs induced by viral infection (Emmott et al. 2019; Diaz et al. 2002), the details of the role of this modification in virus infection remain poorly understood.

Another extensively studied post-translational modification on the ribosome is ubiquitylation, or covalent bonding of ubiquitin to substrate proteins for disposal by the proteasome (degradative ubiquitylation) or alteration of the function of the protein (regulatory ubiquitylation) (Haas et al. 1982; Thrower et al. 2000). Degradative ubiquitylation is important for ribosome-independent function. In fact, excess RPs that are not incorporated into the ribosome are degraded by the proteasome (Lam et al. 2007; Genuth and Barna, 2018). Several RPs have been shown to be dynamically ubiquitylated in response to cellular conditions; RPS2, RPS3, and RPS20, for instance, undergo regulatory ubiquitylation during the unfolded protein response (UPR) in yeast, fruit fly, and human cell lines (Higgins et al. 2015). Notably, the ubiquitination of RPS20 was found to be specifically required for viral replication and synthesis of poxvirus proteins (DiGiuseppe et al. 2018). In addition to ubiquitin, other related proteins have been found to modify the ribosome.

RPL26, for instance, is the principal target of UFM1 conjugation, a ubiquitin-related modification (ufmylation), and UFMylated RPL26 is highly enriched on ER membrane-bound ribosomes and polysomes (Walczak et al. 2019; Wang et al. 2019). UFM1 is also conjugated to RPS3, RPS20, and RPL10 (Simsek et al. 2017). The overlap of ufmylation and ubiquitylation on RPS3 and RPS20 also occurs, and this suggests that certain RPs have combinatorial modifications. O-GlcNAcylation modification was also found to be activated in response to adverse stress to protect cellular proteins from damage (Zachara and Hart 2004, 2006; Slawson et al. 2006). In the stress response, O-GlcNAc-modified proteins are prominent components of stress granules, including small and large ribosomal subunit proteins (RPS3, 9, 11 and 24, and RPL6, 13a, 14, 30 and 36a-like) and the ribosome-associated protein RACK1 (Ohn et al. 2008). Although the effect of RP O-GlcNAcylation on viral infection has been as yet little studied, we can to some extent understand RP O-GlcNAcylation under viral infection through other forms of cellular stimulation, and start to develop an understanding of the possible role of post-translational modification of RPs in antiviral strategy.

The redistribution of RPs to different subcellular compartments

Although RPs are all synthesized in the cytoplasm, they assemble into functional subunits in different subcellular compartments (Kressler et al. 2010; Li 2019). Sometimes, ribosomal proteins change their localization under virus infection to exercise functions outside the ribosome. RPL22, for instance, is translocated from the nucleoli to the nucleoplasm and colocalized with ICP4 in infection by HSV-1. The location change of RPL22 plays a role in the regulatory functions expressed by ICP4 (Leopardi and Roizman, 1996). In another example of similar function, after DENV infection, RPL18 is redistributed to the perinuclear region for regulation of viral replication (Cervantes-Salazar et al. 2015). In eukaryotic cells, acidic ribosomal protein RPLp0 binds two P1/P2 protein heterodimers to form a pentameric P-stalk (Ballesta et al. 1996; Naganuma et al. 2007). Eukaryotic RPLp1 and RPLp2 proteins also exist in free form in the cytoplasm, and the exchange between the ribosome-bound RPLp1 and RPLp2 proteins and the cytoplasmic pools is thought to regulate the activity of the ribosome (Lee et al. 2010). This property may lead to changes in the localization of RPLp1/2 in the ribosome and cytoplasmic pools under stress conditions. Viral infection is one of numerous possible stress stimuli, so viral infection may cause RPLp1/2 to produce this subcellular compartment exchange to affect virus-host translation regulation. Under nucleolar stress induction, RPLp0 accumulates in the cytoplasm of mammalian cells as a free, ribosome-unbound protein (Deryło et al. 2018). A ribosome-free pool of RPLp0 has been shown to be a population of proteins released from pre-existing ribosomes. The presence of RPLp0 on the ribosome seems to be affected in stressed cells, and it might be considered as a regulatory element responding to environmental fluctuations. In addition, the mitochondrial RPs (MRPs) are encoded by nuclear genes and then imported into mitochondria for assembly; they are responsible for the translation of 13 mitochondrial mRNAs (Christian and Spremulli 2012). Mitochondrial RPL18 acts as a critical regulator of the stress response and generates a cytosolic isoform in a stress-dependent manner. The cytosolic RPL18 is incorporated into the 80S ribosome and facilitates ribosome engagement in heat-shock protein (HSP) mRNA translation to escape from the shutoff of global protein synthesis during stress (Zhang et al. 2015).

RPs cooperate with RNA helicase to facilitate virus initiation translation

Accumulating evidence has revealed the roles of RPs belonging to the large 60S subunit in regulating selective translation of specific mRNAs, although they are primarily involved in catalyzing peptide-bond formation (Wilson et al. 2012). A previous study by the present author identified RPL13 as a critical regulator of IRES-driven translation during foot-and-mouth disease virus (FMDV) infection, but found that it is not essential for cellular global translation (Han et al. 2020). Our results support a model whereby the viral IRESs recruit helicase DDX3 downstream of the RPL13 to facilitate IRES-driven translation and viral replication. Specifically, the depletion of DDX3 disrupts binding of RPL13 to the FMDV IRES, whereas the reduction in RPL13 expression impairs the ability of DDX3 to promote IRES-driven translation directly. This work was the first to identify a connection between DDX3 and RPs in modulating viral IRES-dependent translation (Han et al. 2020). DDX3 is well known, however, to play roles in various key aspects of RNA metabolism, including transcriptional regulation, splicing, mRNA export, ribosome biogenesis, and translational regulation (Chuang et al. 1997; Rocak and Linder 2004; Guenther et al. 2018). Improved knowledge about these RNA helicases and their relation to translation initiation could have important implications for the understanding of selective translation of viral mRNA, and thus for the development of effective antivirals.

Translation regulators as specific targets for antiviral design

The strategy of targeting a host factor, instead of the virus directly, could circumvent the danger of resistance in mutation-associated variations and the evolution of new viral

variants after prolonged use of otherwise-promising antiviral drugs. After 60 years of research on ribosomes, the ribosome has emerged as a major player in translational regulation, and its place in the list of potential antiviral therapeutic targets has been reinforced. Targeting the ribosome, either biogenesis or function, may provide an efficient and focused approach for design of antiviral agents.

As our understanding of the function of RBFs and RPs in viral translation has evolved, the design of therapeutic strategies for RBFs and RPs has been explored. Recent structural analysis of prokaryotic and eukaryotic ribosomes has demonstrated that certain molecules, including some antibiotics and chemical inhibitors of translation, can bind to the ribosome (Svetlov et al. 2017; Tereshchenkov et al. 2018). CX-5461, for example, is a ribosomal biogenesis inhibitor that disrupts RNA Pol I—mediated transcription (Drygin et al. 2011), and inhibits viral DNA synthesis and virus production in the early and late stages of the HCMV infection (Westdorp and Terhune 2018). Toyocamycin is a small molecule inhibitor of Rio1 kinase activity (Kiburu et al. 2012); Rio1 is an essential ribosome biogenesis factor required for maturation of 40 S ribosomal subunit (Angermayr et al. 2002). Toyocamycin inhibits ribosome biogenesis to produce antiviral effects (Ríman et al. 1969). Notably, translation of IRES-containing viruses (such as HCV, HTLV-1, CrPV, poliovirus, and adenovirus) is dependent on RPS25 (Landry et al. 2009; Hertz et al. 2013; Olivares et al. 2014), and its activity is highly sensitive to the antibiotic Edeine (Olivares et al. 2014). Picolinic acid (PA) and fusaric acid (FU) disrupt the ZFP motifs of RPS27 or crucial viral proteins to produce antiviral effects (Yu et al. 1995; Everett et al. 1993; Wakefield and Brownlee 1989; Love et al. 1996). Ricin is an RPLp protein inhibitor (May et al. 2012); RPLp1/2 is an essential host factor for flavivirus replication (Campos et al.2017). RACK1 is essential for the translation of many viruses, including HCV, Drosophila C (DCV), Cricket Paralysis (CrpV) (Majzoub et al. 2014), and vaccinia viruses (Jha et al. 2017). Thus, RACK1 inhibitors may be developed as novel antiviral therapeutics. The drug SD-29 and analogues show high efficacy in inhibition of virus proliferation (Ullah et al. 2019). Exploring strategies for targeting RBFs and RPs is a natural path for further study in this field.

Once the function of RBFs and RPs in viral translation is understood, targeting inhibitors will need to be identified, designed, and screened. To accelerate the process of drug discovery for both novel targets and existing targets that suffer from drug resistance, basic platforms for drug design and screening are required. In a recent study, structure-based screening of two million commercially available compounds was used to screen for small molecules to target the RACK1 Y248 phosphorylation site. (As noted, host RACK1 protein is an attractive target for developing broad antiviral drugs.) Dozens of small compounds were identified that could potentially bind to the experimentally determined functional site of the RACK1A protein; the drugs show high efficacy in inhibition of the proliferation of viruses that require RACK1 for translation (Ullah et al. 2019). This approach can be used to study the ribosomal proteins that are essential for the translation of many viruses, and eventually to design broad-spectrum antiviral drugs. Furthermore, depletion of regulatory RBFs and RPs is not essential for basic ribosomal function in experiments, making them potential targets for the design of small molecule antiviral drugs. RNA interference (RNAi) and strategies based on CRISPR/cas9 are also promising approaches in targeting of RBF and RP genes. Of course, projecting forward to the practical application of antiviral drugs, the adverse cell response caused by targeting of RBF and RP genes must be studied in detail.

New approaches to identification of RP production and function

Deciphering the functional details of translation of viral mRNA will require the in-depth scrutiny of RPs. A number of technological efforts have been made over the last decade to facilitate exploration of RP biogenesis and functions. Ribosome profiling is an emerging technique that allows the distribution of ribosome units on each transcript to be obtained, enabling systematic probing of translation and increased sensitivity and efficiency. This method, in conjunction with RNA-seq, has been used to probe the complex viral replication of several viruses (Yang et al. 2015; Irigoyen et al. 2016). Using high-coverage tandem mass tag (TMT) mass spectrometry, the relative monosome and polysome fractions of each RP were compared. A thorough examination of each RP revealed that some RPs (such as RPS9 and RPL11) are more abundant in monosomes than in polysomes (Slavov et al. 2015). TMT technology has been extended to the investigation of potential heterogeneity of RPs. Mass spectrometry has also been improved to address directly and more accurately the possibility of variability in RP stoichiometry. This novel technology, called selected reaction monitoring (SRM)-based proteomics, uses the spiking of samples with known amounts of labeled peptides derived from RPs as a standard for absolute quantification. Using this technology, absolute quantification of 15 RPs isolated from polysomes was assessed and 4 RPs, RPL10A, RPL38, RPS7, and RPS25, were identified as being substoichiometric in murine ESC ribosomes (Shi et al. 2017). Based on this technology, the heterogeneity in ribosome composition within a single cell type and a single polysome profile fraction was revealed for the first time. These approaches provide a starting point in the attempt to identify and quantify each RP expression profile in cells challenged with viruses,

and at different infectious stages. In a recent study, both the small and large ribosomal subunits in mouse ESCs were endogenously tagged, and affinity enrichment for each of the tagged ribosomal subunits was performed to define the intersection of the two separate ribosomal subunit datasets. This has led to the identification of ribosome-associated proteins (RAPs), which fall into unexpected functional categories, such as energy metabolism, cell cycle, and key protein and RNA modification enzymes (Simsek et al. 2017). This method may facilitate identification of a series of proteins (such as RAPs) that are specifically recruited to ribosomes with the assistance of RPs, and act as potential targets for antiviral therapeutic design. Technical limitations have thus far impeded the study of selective translation mediated by RPs in viral infection, and considerable research will be required before clinical application of viral therapeutics based on the targeting of RPs.

Conclusions and path forward

Historically, the ribosome has been viewed as a complex ribozyme, and ribosome activity has been considered to be highly regulated. Although the concepts of ribosome heterogeneity and specialization at the level of core RPs are still in infancy, solid data have been published in various areas, offering convincing evidence that the ribosome plays a constitutive role as well as a regulatory function in translation. Moreover, constitutive components of the ribosome may perform more specialized activities by virtue of their interactions with specific mRNA regulatory elements, such as IRESs. These findings add numerous layers of subtlety to the conventional interpretation of translational regulation.

Viruses depend on host cell structures and translation systems to complete their life cycle. In order to survive in the host cell and achieve rapid replication and proliferation, viruses have developed various mechanisms to allow the selective translation of viral mRNA and repress cellular mRNA translation. Inducing host translation shutoff is a strategy used by many viruses to optimize their replication and spread by fostering viral protein synthesis and crippling host antiviral responses. In this process, some RPs are activated to promote the translation of specific transcripts, and thus the virus can still synthesize its own proteins to optimize their replication and spread when host translation is shut off.

In this review, we focus on the important role of RP production and function in viral or host translation processes that support viral replication and infection. Understanding the research on the specialized RBFs and RPs utilized by a virus can deepen the understanding of selective translation, and expand the depth and breadth of the field of virus-host interactions. This research, data, and theoretical evidence will facilitate the identification of antiviral targets and the eventual design of antiviral drugs, and advance the development of therapeutic strategies to produce optimal antiviral agents for effective control of viral diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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