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Viral modulation of stress granules

Fernando Valiente-Echeverría[a,b], Luca Melnychuk[a,c], Andrew J. Mouland[a,b,c,*]

[a] HIV-1 RNA Trafficking Laboratory, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montréal, Québec H3T 1E2, Canada
[b] Department of Medicine, Division of Experimental Medicine, McGill University, Montréal, Québec H3A 1A3, Canada
[c] Department of Microbiology and Immunology, McGill University, Montréal, Québec H3A 2B4, Canada

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ABSTRACT

Following viral infection, the host responds by mounting a robust anti-viral response with the aim of creating an unfavorable environment for viral replication. As a countermeasure, viruses have elaborated mechanisms to subvert the host response in order to maintain viral protein synthesis and production. In the last decade, several reports have shown that viruses modulate the assembly of stress granules (SGs), which are translationally silent ribonucleoproteins (RNPs) and sites of RNA triage. This review discusses recent advances in our understanding of the interactions between viruses and the host response and how virus-induced modulations in SG abundance play fundamental roles in dictating the success of viral replication.

1. Introduction

Exposure of cells to environmental stress (e.g., heat shock, UV irradiation, hypoxia, endoplasmic reticulum (ER) stress and viral infection) trigger a rapid translational arrest generating polysome disassembly (Anderson and Kedersha, 2002). This event triggers a molecular triage, where the affected cell must make a decision on the fate of mRNA that is released from polysomes: decay or silencing (Anderson and Kedersha, 2008). For these events, cells have elaborated different classes of RNA granules named processing P-bodies (PBs) or stress granules (SGs) that contribute to the regulation and lifecycle of mRNAs. Both PBs and SGs contain share proteins and are assembled in cells subjected to stress, but differ in: (i) only PBs are observed in unstressed cells, (ii) SG assembly typically requires phosphorylation of translation initiation factor eIF2α, but not PB assembly (Fig. 1), and (iii) PBs contain proteins involved in mRNA decay, whereas SGs contain proteins of translation initiation complex (Eulalio et al., 2007).

PBs are cytoplasmic structures that, unlike SGs, are responsible for mRNA decay, RNA-mediated gene silencing (microRNA and siRNA-based gene silencing) and mRNA surveillance (or RNA quality control) (Beckham and Parker, 2008). PBs were discovered by Bashkirov et al. (1997) and they showed that XRN1, a 5′–3′ exoribonuclease, was localized in small granular structures within the cytoplasm. Other proteins related to mRNA degradation were also found to localize to this granules, such as a deadenylase (CCR4), decapping enzymes Dcp1 and Dcp2 as well as the activators of decapping Dhh1/p54/Rck/DDX6, Pat1, Scd6/RAP55, Edc3, Hedls and Lsm1–7 complex (Eulalio et al., 2007; Ingelfinger et al., 2002; van Dijk et al., 2002). Moreover, PBs can contain mRNAs and proteins involved in Nonsense-Mediated Decay (NMD) (e.g., SMG5, SMG7, and UPF1) (Fukuhara et al., 2005; Unterholzner and Izaurralde, 2004) and components of the *RNA-induced silencing complexes* (RISC) (e.g., argonaute, microRNA and GW182) (Liu et al., 2005; Rehwinkel et al., 2005) (Fig. 2).

On the other hand, SGs were first observed in the cytoplasm of plant cells exposed to heat shock (Nover et al., 1983). SGs are translationally silent ribonucleoproteins and serve as storage sites of mRNAs and proteins (Anderson and Kedersha, 2006) (Fig. 2), while other functions also have been discussed (Thomas et al., 2011). SGs typically contain poly(A)+mRNA, 40S ribosomal subunits, eIF4E, eIF4G, eIF4A, eIF4B, poly(A)-binding protein (PABP1), eIF3, eIF2, p54/Rck/DDX6, and many other RNA-binding proteins that regulate mRNA structure and function, including human antigen R (HuR), Staufen 1, polysomal ribonuclease 1 (PMR-1), Smaug, tristetraprolin (TTP), T-cell restricted intracellular antigen 1 (TIA-1) and TIA-1-related protein (TIAR), Fragile X Mental Retardation Protein (FXMR/FXR1), Ras-Gap SH3-binding protein (G3BP-1), cytoplasmic polyadenylation binding protein (CPEB) and Survival of Motor Neurons (SMN) protein, although the composition can vary (Anderson and Kedersha, 2006) (listed in Table 1).

During a stress response, cells induce a shut-off of cellular protein synthesis and subsequently promote SG assembly (Anderson and Kedersha, 2009). Different pathways in SG assembly have

* Corresponding author at: HIV-1 RNA Trafficking Laboratory, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montréal, Québec H3T1E2, Canada. Tel.: +1 514 340 8260; fax: +1 514 340 7502.
E-mail address: andrew.mouland@mcgill.ca (A.J. Mouland).

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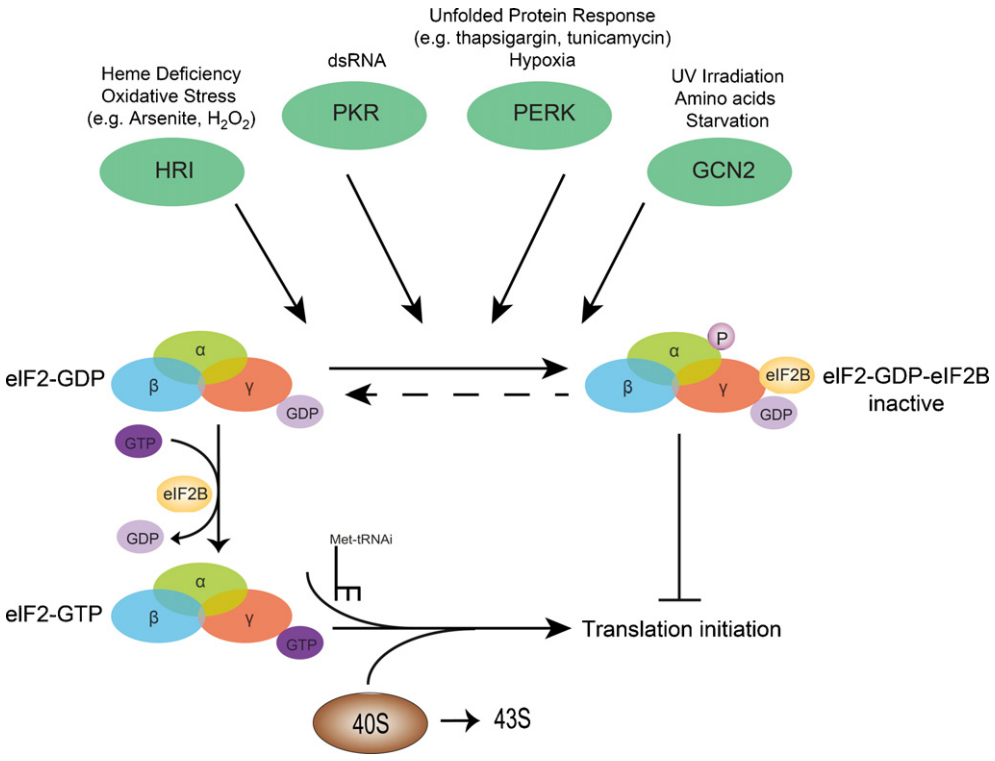

Fig. 1. Control of translation by eukaryotic initiation factor 2 (eIF2). eIF2 bound to GDP (eIF2-GDP) is recycled to the active eIF2-GTP by a reaction catalyzed by eIF2B. Once recycled, eIF2-GTP forms a ternary complex with initiator-methionine tRNA (Met-tRNAi) and 40S ribosome resulting in 43S pre-initiation complex. Four kinases activated by hemin deficiency/oxidative stress (HRI), viral infection (PKR), endoplasmic reticulum stress/hypoxia (PERK/PEK) and amino acid starvation/UV irradiation (GCN2); can phosphorylate eIF2 subunit α, stabilize eIF2-GDP–eIF2B complex (inactive) and prevents eIF2 recycling. These events result in a shut-off of the host protein synthesis and subsequently SG assembly (Fig. 2, i).

been described. The most popular pathway is the phosphorylation of the critical translation initiation factor, eIF2α by a family of four serine/threonine kinases HRI, PKR, PERK/PEK and GCN2. HRI (eIF2αK1) is activated in heme deprivation and oxidative stress (Han et al., 2001); PKR (eIF2αK2) is activated by viral infection (Williams, 2001); PERK/PEK (eIF2αK3) is activated in the presence of unfolded proteins in the endoplasmic reticulum (ER) and during hypoxia (Harding et al., 2000); and GCN2 (eIF2αK4) is activated during amino acid starvation and UV irradiation (Jiang and Wek, 2005). Each kinase causes the phosphorylation of the α-subunit of eIF2 at Ser52, which implies the tight binding with eIF2B, inhibiting the exchange of GDP for GTP (Fig. 1). Therefore, there is a decrease in translation tertiary complex assembly (eIF2/GTP/Met-tRNA) which suppresses the initiation of translation and promotes SG assembly (Fig. 2, step i) (Kedersha et al., 2002). Other mechanisms independent of the phosphorylation of eIF2α have also been explored. Hippuristanol and Pateamine A, drugs that inhibit the helicase activity of eIF4A, are able to induce the assembly of SGs (Fig. 2, step ii) (Dang et al., 2006; Mazroui et al., 2006). As well, the overexpression of SG markers (Anderson and Kedersha, 2008), such as TIA1 (Kedersha et al., 1999) or G3BP-1 (Tourriere et al., 2003), can trigger the assembly of SGs (Fig. 2, step iii).

The activation of eIF2α kinases by viral infection may result in the inhibition of cellular protein synthesis (Walsh and Mohr, 2011) and/or promotion of autophagy, process involving lysosomal-dependent recycling of intracellular components (Talloczy et al., 2002). Moreover, some viral proteins can bind eIF4A (Aoyagi et al., 2010; Page and Read, 2010). All of these mechanisms induce SG assembly (i.e., shut-off of cellular protein synthesis), but the viruses have found ways to bypass the hostile environment generated by the cell to ensure their survival. In the last decade, several studies have also demonstrated that the assembly of SGs can be dramatically influenced by viruses: the induction and blockage of SG assembly mediated by viral infections have both been described as means to promote virus replication (Beckham and Parker, 2008; Montero and Trujillo-Alonso, 2011; White and Lloyd, 2012). In this review we will summarize the current understanding that exists between different virus families and the regulation of stress granules.

Table 1
Stress granule components.

Protein	Reference
40S	Kedersha et al. (2002)
eIF2	Kedersha et al. (2002)
eIF3	Kedersha et al. (2002)
eIF4AI	Kedersha et al. (2002)
eIF4E	Kedersha et al. (2002)
eIF4G	Kedersha et al. (2002)
PABP-1	Kedersha et al. (1999)
p54/RCK/DDX6	Wilczynska et al. (2005)
TIA-1/TIAR	Gilks et al. (2004)
TTP	Stoecklin et al. (2004)
HuR/HuD	Kedersha et al. (1999)
Staufen 1	Thomas et al. (2009)
SMN	Hua and Zhou (2004)
G3BP-1	Tourriere et al. (2003)
Smaug	Baez and Boccaccio (2005)
FXMR/FXR1	Mazroui et al. (2006)
CPEB	Wilczynska et al. (2005)
PMR1	Yang et al. (2006)
RSK2	Eisinger-Mathason et al. (2008)
RACK1	Arimoto et al. (2008)
TRAF2	Kim et al. (2005)
FAST	Kedersha et al. (2005)
BRF1	Kedersha et al. (2005)

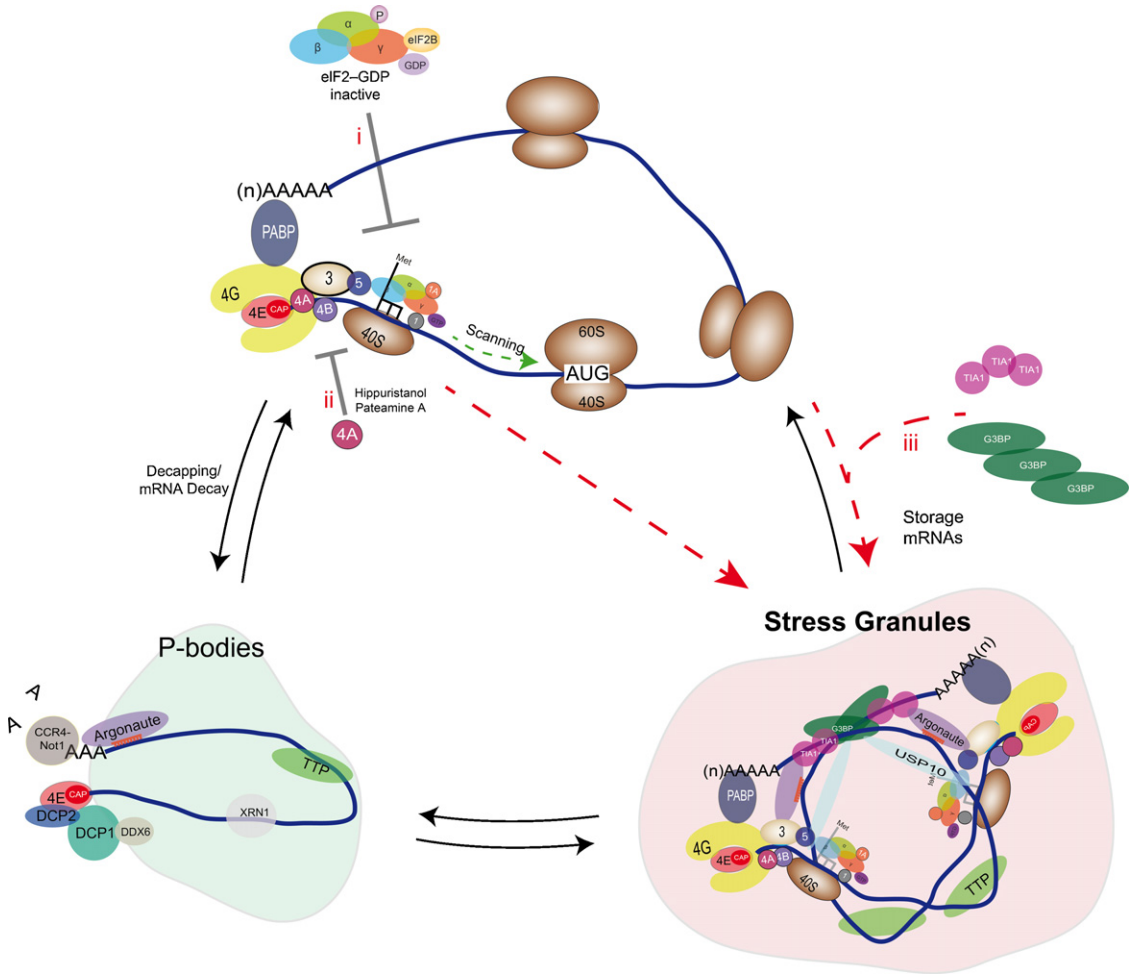

Fig. 2. SG assembly pathways. Polysomes disassembly can lead to the assembly of cytoplasmic granules know as processing P-bodies (PBs) or stress granules (SGs). If deadenylation (e.g., CCR4/Not1), destabilization (e.g., TTP/XRN1) and decapping (e.g., DCP1/DCP2) complex; and even RISC (Ago) complex are recruited to mRNA, these will be targeted to PBs. Conversely, if TIA-1/TIAR or proteins such as G3BP/USP10 are recruited to the stalled initiation complexes, these will be directed to SGs. Different pathways in SG assembly are described (in red): (i) phosphorylation of eIF2α induced by the exposure to different stress inducers (e.g., arsenite and thapsigargin) (Fig. 1); (ii) Hippuristanol and Pateamine A, drugs that inhibit the helicase activity of eIF4A altering ATP binding or ATPase activity; and (iii) the overexpression of SG markers, such as G3BP or TIA-1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Virus-mediated blockade of SG assembly

In 2002, the first evidence was reported showing an interaction between viruses and what we understand to be protein components of SGs. Li et al. showed that the negative strand 3′ terminal stem–loop structure present in the genome of West-Nile Virus (WNV) interacts with two SG markers, TIA-1 and TIAR (Li et al., 2002). In support of the necessity for these virus–host interactions, WNV replication was reduced when TIAR$^{-/-}$ cells were infected (Li et al., 2002). WNV is a neurotropic *flavivirus* responsible for viral meningoencephalitis which has an enzootic cycle between mosquitoes and birds, but can infect amphibians, reptiles, horses and humans (Dauphin et al., 2004). Moreover, Emara et al. expanded these observations to other members of the same viral *flaviviridae* family, where TIA-1/TIAR were shown to co-localize with viral replication complexes (dsRNA and NS3) in both WNV- and dengue virus-infected cells (Emara and Brinton, 2007). SGs can be induced in mammalian cells by several drugs (Kedersha and Anderson, 2007), apparently as a consequence of the phosphorylation of eIF2α. In order to determine if viral infection would have any effect on SG assembly, Baby Hamster Kidney (BHK) cells were infected with wild-type WNV and subjected to arsenite-mediated oxidative stress. Infected cells were found to be resistant to SG induction (Emara and Brinton, 2007). However, recent studies showed that chimeric WNV produces high levels of an early viral RNA (W956IC), allowing PKR activation and subsequent induction of SG, likely due to translational arrest (Courtney et al., 2012).

Another *flavivirus*, Hepatitis C Virus (HCV), the major etiologic agent of hepatitis C in humans, is able to disrupt PB assembly but at the same time, promote SG assembly during the course of viral infection (Ariumi et al., 2011). However, late in HCV infection corresponding to 48 h post-infection, G3BP-1 and DDX6, both components of SG (Table 1), are found to co-localize with the HCV core, resulting in the suppression of SG assembly. This blockade to SG assembly was found to be due to an interaction between G3BP-1 and the HCV non-structural protein, (NS)5B and the 5′ end of the HCV minus-strand RNA (Yi et al., 2011). Thus, as shown in the examples above, through sequestration of factors essential for the assembly of SGs, several viruses have elaborated mechanisms to impose a blockade to SG assembly.

Some viruses inhibit cap-dependent translation (hence host cell mRNA translation) to ensure the synthesis of their own proteins. Pelletier et al. discovered that the translation of the uncapped picornaviral mRNA is mediated by an RNA structure known as the internal ribosome entry site, IRES, at the 5′ end of the viral RNA (Pelletier et al., 1988). Infection by poliovirus (PV), the etiologic agent of paralytic disease known as poliomyelitis, induces the inhibition of cap-dependent translation initiation by the cleavage of

the translation initiation factors eIF4GI, eIF4GII, and PABP mediated by viral proteinases (Gradi et al., 1998; Kuyumcu-Martinez et al., 2002). SG assembly is induced at a very early time post-PV infection (at approximately 2–4 h), but later, SGs disappear because the same viral 3C proteinase (3Cpro) cleaves G3BP-1, but not TIA-1 or TIAR, and thereby prevents SG assembly (White et al., 2007). The SGs found in PV-infected cells contain viral RNA and TIA-1, but are compositionally distinct since they exclude well-described SG components such as G3BP-1, PABP, and eIF4G, all of which are eventually cleaved by 3Cpro (Piotrowska et al., 2010; White and Lloyd, 2011). Furthermore, PV infection also disrupts the assembly of PBs. Also during PV infection, Xrn1, Dcp1a and Pan3, three factors involved in mRNA decapping, degradation and deadenylation, respectively, undergo degradation or cleavage by the viral 3Cpro (Dougherty et al., 2011).

Likewise, Cricket Paralysis Virus (CrPV) infection in *Drosophila* cells leads to a rapid shut-off of host protein synthesis concomitant with phosphorylation of eIF2α (Wilson et al., 2000). Because these characteristics are common to the induction of SGs, Khong et al. investigated the assembly of SG after CrPV infection. Through an immunofluorescence assay, the authors showed that Rox8 and Rin, *Drosophila* SG marker homologs of TIA-1 and G3BP-1, respectively, do not aggregate in CrPV infected cells, even in the presence of SG inducers such as heat shock, oxidative stress and Pateamine A. It was also demonstrated that CrPV viral 3C proteinase is sequestered to SGs under cellular stress but not during virus infection (Khong and Jan, 2011).

Another *picornavirus*, Theiler's murine encephalomyelitis virus (TMEV) which causes a demyelinating disease similar to multiple sclerosis in the central nervous system, also inhibits SG assembly. Borghese et al. showed that TMEV infection induces SG assembly, but the expression of the leader (L) protein during infection was sufficient to inhibit SG assembly induced by arsenite-mediated oxidative stress or by thapsigargin-mediated ER stress. Unlike the effects induced by PV 3C proteinase, G3BP-1 was not cleaved by TMEV and was in fact found in SGs post-TMEV infection (Borghese and Michiels, 2011).

For efficient protein synthesis, mRNA circularization is required during translation. PABP, that is bound to poly (A) 3′ tail, interacts with eIF4GI at the 5′, causing circularization of the mRNA by linking the 5′ and 3′ mRNA ends, increasing the binding of eIF4E to the cap (Lopez-Lastra et al., 2010). Rotavirus, the *causative agent* of a common infantile gastroenteritis, subverts the host translation machinery at this step. Because rotavirus mRNAs are capped but lack poly(A) tails, the virus-encoded protein, non-structural (NS) P3, binds to a consensus RNA sequence in the 3′ end of viral mRNA, enabling mRNA circularization by interaction with eIF4GI (Piron et al., 1998). As a consequence, a shut-off of host protein synthesis ensues and thereby provides an advantage for viral protein synthesis. In infected cells, Montero et al. found that eIF2α is phosphorylated during the entire virus replication cycle but this does not have an impact in the formation of viroplasms (cytoplasmic viral factories found in rotavirus-infected cells) or viral replication and surprisingly, SG assembly was not induced. One possibility for explain this observation may be due to PABP, a component of SG (Table 1), is able to translocate from the cytoplasm to the nucleus in rotavirus infected cells in a NSP3-dependent manner (Montero et al., 2008).

Instead, Junin virus (JUNV), that is responsible for Argentine hemorrhagic fever, is able to impair the phosphorylation of eIF2α. Linero et al. showed that in JUNV-infected Vero cells exposed to arsenite-mediated oxidative stress, eIF2α phosphorylation was impaired but this did not lead to the induction of SG assembly (Linero et al., 2011). Furthermore, the JUNV nucleoprotein (N) and/or the glycoprotein precursor (GPC) was responsible for this virus-induced blockade to SG assembly. Rather, when JUNV-infected cells were treated with hippuristanol, an eIF4A-helicase activity inhibitor that induces SGs in an eIF2α-independent manner (Mazroui et al., 2006), SG assembly was observed in 100% of cells indicating that JUNV affects an unidentified event downstream of eIF2α phosphorylation or the integrity of viral mRNAs on polysomes (Linero et al., 2011).

Another virus that efficiently shuts off host protein synthesis is influenza A virus (IAV) (Kash et al., 2006). IAV is an animal pathogen that causes severe respiratory disease and pandemics in humans around the world. Viral transcription involves a cap-snatching mechanism during which a nucleotide sequence between 10 and 20 nt, including the 5′ cap structure, is cleaved from the 5′ end of cellular mRNAs. This sequence is used to prime transcription on the viral genome and is ultimately used during translation initiation of viral mRNAs (Lopez-Lastra et al., 2010). Additionally, IAV encodes cap-binding proteins that are able to preferentially recognize capped viral mRNAs. The influenza non-structural protein 1 (NS1) binds eIF4GI and PABP-1, thus stimulating the assembly of the translation initiation complex on capped IAV mRNAs (Lopez-Lastra et al., 2010). IAV actively suppresses SG assembly during viral infection, thereby allowing translation of viral mRNAs. Complete inhibition of SG assembly is dependent on the function of NS1 and its ability to inhibit PKR, the double-stranded RNA-activated protein kinase (Khaperskyy et al., 2011).

Recently, *retroviruses* such as the human immunodeficiency virus type-1 (HIV-1) and human T-cell lymphotropic virus type-1 (HTLV-1) were shown to impose a blockade to SG assembly in infected cells. Recent work from the authors' laboratory showed that HIV-1 preferably assembles ribonucleoprotein complexes to which Staufen1, the viral genomic RNA and the structural protein Gag are recruited, called Staufen1 HIV-1-dependent RNPs (SHRNPs). These were compositionally different than SGs since they did not contain many of the classical SG marker proteins G3BP-1, eIF3, TIA-1, TIAR, HuR, PABP-1, but contained Staufen1. The assembly SHRNPs during the late stages of viral replication is believed to impose a blockade to the assembly of SGs but to favor the encapsidation of HIV-1 genomic RNA into assembling virus (Abrahamyan et al., 2010; White and Lloyd, 2012). Follow-up work, reported at the last International Nucleocapsid (NC) Meeting in Barcelona, Spain in September 2011, now demonstrates that the viral Gag protein controls the kinetics of SG assembly and interferes with the cellular stress response pathway (Valiente-Echeverría et al., unpublished). The *oncoretrovirus*, HTLV-1 elicits a blockade to SG assembly in a different manner and this was found to be mediated by the viral regulatory protein, Tax. Legros et al. observed that Tax relocated from the nucleus to the cytoplasm in response to environmental stress. While Tax is present in the cytoplasm, it interacts with histone deacetylase 6 (HDAC6), a critical component of SGs (Kwon et al., 2007), and thereby impairs SG assembly (Legros et al., 2011). While the details on the mechanisms by which viruses elicit favorable environments in which to replicate will require further work, the sequestration of critical factors for the induction of SGs by viral proteins appears to be an increasingly studied area of research and should yield important new information on how viruses gain control over host cell biology.

While all of the examples described above belong to RNA viruses, Herpes simplex virus (HSV) and Cytomegalovirus (HCMV) are the only members of the DNA virus family that have been shown to regulate SG assembly. HSV-1 causes a shut-off of host cell protein synthesis by the virion host shutoff (Vhs) protein and subsequently induces degradation of cellular RNAs (Kwong and Frenkel, 1987). Several Adenosine–Uracil (AU)-rich binding proteins that promote mRNA stability, such as TIA-1/TIAR, and TTP (Bevilacqua et al., 2003), were upregulated in HSV-1 infected cells (Esclatine et al., 2004). TTP and TIA-1/TIAR were activated during

Table 2
SG assembly induction/inhibition by different viruses.

Virus family	Common name	SG induction	SG blockage	Mechanism	Reference
Herpesviridae	Herpes Simplex virus-1 (HSV-1)	No	nd[a]	Vhs interact with TTP	Esclatine et al. (2004)
	Cytomegalovirus (HCMV)	No	Yes	Induce UPR but viral translation is maintained	Isler et al. (2005a,b)
Reoviridae	Rotavirus	No	Yes	May be due by PABP is relocates from the cytoplasm to the nucleus	Montero et al. (2008)
	Mammalian orthoreovirus (MRV)	Yes[b]	Yes[c]	Induce SG by eIF2α phosphorylation	Smith et al. (2006)
Flaviviridae	West Nile virus (WNV)	No	Yes	3′end viral genome interact with TIA-1/TIAR	Li et al. (2002)
	Dengue virus (DV)	No	Yes	TIA-1/TIAR colocalize with replication complex	Emara and Brinton (2007)
	Hepatitis C Virus (HCV)	Yes[b]	Yes[c]	G3BP-1 interact with NS5B and 5′end viral genome	Yi et al. (2011)
Picornaviridae	Poliovirus (PV)	Yes[b]	Yes[c]	3Cpro cleaves G3BP-1	White et al. (2007)
	Theiler's murine encephalomyelitis (TMEV)	No	Yes	Leader (L) protein inhibit SG assembly	Borghese and Michiels (2011)
Dicistroviridae	Cricket paralysis virus (CrPV)	No	Yes	3Cpro is sequestered to SG	Khong and Jan (2011)
Togaviridae	Semliki Forest Virus (SFV)	Yes[b]	Yes[c]	Induce SG by eIF2α phosphorylation	McInerney et al. (2005)
	Rubella virus (RUBV)	Yes	nd[a]	Accumulation of G3BP	Matthews and Frey (2012)
Coronaviridae	Mouse hepatitis coronavirus (MHV)	Yes	nd[a]	Induce SG by eIF2α phosphorylation	Raaben et al. (2007)
Arenaviridae	Junin virus (JUNV)	No	Yes	N and GPC proteins block SG assembly by eIF2α phosphorylation	Linero et al. (2011)
Orthomyxoviridae	Influenza (IAV)	No	Yes	NS1 protein inhibit PKR	Khaperskyy et al. (2011)
Paramyxoviridae	Respiratory Syncitial virus (RSV)	Yes	nd[a]	Induction PKR dependent	Lindquist et al. (2011)
Retroviridae	Human T cell Leukemia virus type-1 (HTLV-1)	No	Yes	Tax interact with HDAC6	Legros et al. (2011)
	Human immunodeficiency virus type-1 (HIV-1)	No	Yes	Staufen 1 and Gag block SG assembly	Abrahamyan et al. (2010)

[a] Not determined.
[b] Showed in early stage of infection;
[c] Showed in late stage of infection.

the infection and accumulated in the cytoplasm, but only TTP was able to interact with Vhs. As a consequence, SGs were not observed after infection (Esclatine et al., 2004). More recently, Finnen et al. have shown that HSV-2 infection blocks SG accumulation in cells exposed to arsenite-mediated oxidative stress, but not in cells exposed to Pateamine A, a drug that induces SG assembly in an eIF2α-independent manner (Finnen et al., 2012). These results were similar to those found in JUNV infected cells described above (Linero et al., 2011). On the other hand, HCMV infection induces an unfolded protein response (UPR), activates PERK, but eIF2α phosphorylation levels were limited and viral RNA translation was maintained (Isler et al., 2005b). Likewise, the same group showed that SG assembly was suppressed in HCMV infected cells treated with the ER stressor, thapsigargin (Isler et al., 2005a). As discussed in the previous section, viruses have chosen different mechanisms to inhibit the SG assembly to ensure efficient and unmitigated replication.

3. Virus-mediated induction of SG assembly

Some studies have demonstrated that the SG assembly is not always correlated with a shut-off of host protein synthesis (Kimball et al., 2003; Loschi et al., 2009). Moreover, other authors have showed that SGs could sequester apoptotic molecules favoring cell survival upon exposure to certain types of stress such as heat shock (Kim et al., 2005; Tsai and Wei, 2010). Thus, a virus-mediated induction of SG assembly also represents a strategy employed by some viruses to ensure replication.

Respiratory Syncytial Virus (RSV), which is responsible for lower respiratory tract illnesses in both infants and the elderly, induces SGs during the course of infection (Lindquist et al., 2010). Lindquist et al. showed the correlation between higher viral protein levels and the presence of SGs in infected cells. In addition, G3BP$^{-/-}$ cells, that are unable to generate SGs because of a disrupted *g3bp* gene locus, exhibited diminished RSV replication (Lindquist et al., 2010). However, a later study by the same group concluded that the stress response may not play an important role in viral replication. They did not see a difference in viral replication in cells that were not able to elicit a stress response because PKR was depleted by siRNA (Lindquist et al., 2011). This later study also noted that RSV infection does cause eIF2α phosphorylation and PKR is needed to induce SGs during viral infection. These results indicate that the assembly of SG neither aids nor interferes with the replication of this virus.

The role of the stress response involving SGs in the *Reoviridiae* family of viruses has been shown to be implicated in viral replication. Mammalian orthoreovirus (MRV) infection in humans is usually asymptomatic or associated with symptoms of a common cold. During the early stages of infection, MRV induces SG assembly and the expression of ATF4, a transcription factor, through eIF2α phosphorylation (Smith et al., 2006). The assembly of SGs creates a competitive advantage for the viral mRNA to be translated because cellular mRNAs are sequestered in SG. When ATF4 is expressed in MRV infected cells, viral production increases by up to 100-fold (Smith et al., 2006). A later study implicated a role for SG assembly in viral replication since SG formation occurs after viral uncoating but before viral mRNA transcription (Qin et al., 2009). Qin et al. (2011) found that viral mRNAs escape translational inhibition when SGs are disrupted and viral translation occurs in the presence of high levels of phosphorylated eIF2α in a manner that is independent of PKR inhibition. This study also mentions that MRV-infected Cos7 cells are able to block the assembly of SGs induced by arsenite-mediated oxidative stress later in infection (Qin et al., 2011). The implication of these findings is that the stress response and the resulting assembly of SGs must be involved in the early stages of the viral replication cycle but is ultimately detrimental to the virus if it is not able to disassemble SG during later stages of infection.

Semliki Forest Virus (SFV), which causes lethal encephalitis in rodents, seems to modulate the cellular stress response in a similar fashion than MRV. Upon infection, SFV is able to induce the phosphorylation of eIF2α and promote SG assembly in mouse embryo fibroblasts (MEF) (McInerney et al., 2005). Despite a shut-off of host

protein synthesis during these events, SFV is still able to translate its mRNA due to a translational enhancer element present in the viral genome. This study also indicated that areas around viral RNA in the cytoplasm were devoid of SGs. This observation likely indicates that viral proteins or viral RNA could locally disassemble SG to favor viral translation and this was shown to correlate with increased vRNA levels (McInerney et al., 2005).

The theme of utilizing the stress response to shut-off of host protein synthesis appears once again in *Coronaviridae*. The mouse hepatitis coronavirus (MHV), which is closely related to the SARS coronavirus, has been shown to subvert the host translation machinery through eIF2α phosphorylation (Raaben et al., 2007). eIF2α phosphorylation also leads to the assembly of SG and PB. A genome wide microarray analysis of regulated mRNAs in MHV-infected LR7 cells revealed the decrease in the expression of many cellular mRNAs, which may be due to an increase in PBs activity and function (Raaben et al., 2007). Likewise, viral RNAs transcripts make up 40% of total RNA in the cell, so the virus may be overloading the host cell cytoplasm to ensure that its transcripts will be translated (Raaben et al., 2007). However, the authors come to the conclusion that the inhibition of cellular translation is not beneficial to the virus since in systems lacking the ability to inhibit cellular translation, viral production did not change and thus, the assembly of SG in MHV-infected cells does not appear to dramatically favor viral replication (Raaben et al., 2007).

Finally, Rubella virus (RUBV) infection generates aggregates of G3BP-1 in the cytoplasm (Matthews and Frey, 2012). These aggregates differ from typical SG because they do not contain proteins such as PABP and TIA-1 (Table 1). RUBV is a positive strand RNA where viral replication is mediated for intermediary double stranded RNA (dsRNA). Matthews et al. found that G3BP-1 does not overlap with dsRNA, but rather colocalizes with viral ssRNA in perinuclear clusters (Matthews and Frey, 2012), suggesting that these may represent sites of encapsidation (Beatch and Hobman, 2000).

4. Conclusions and future directions

Despite an intensifying research focus to understand the relationships between the cytoplasmic RNPs called SG and virus replication (refer to Table 2), many questions remain to be answered in this growing field of virology. The roles for many SG components (Table 1) that have been found to participate in viral replication either by inclusion or exclusion still remain incompletely defined in host cell biology. As well, the literature has only touched the surface as to how viruses hijack and commandeer SG components. In several cases in which SG assembly is shown to be inhibited, it remains unclear if viruses block the assembly or induce the disassembly of SG. There is also a need to determine at what level viruses are hijacking or co-opting the host cell stress responses that exhibit SG. There is also a need to understand how SG may lead to deleterious effects if they remain present during viral infection. Indeed, further characterization of a virus' ability to overcome the inhibition of SG assembly or induce their assembly to prevent translation of host mRNAs may be beneficial in developing new anti-viral drugs that could be useful against multiple viruses. Anti-cancer drugs such as etoposide, bortezomib and doxorubicin, do induce SG assembly, however their roles as anti-virals are not known (Arimoto et al., 2008; Fournier et al., 2010; Morita et al., 2012). The many mechanisms by which viruses inhibit or induce SG may pose a problem to developing a broad anti-viral drug targeting SG. Viruses such as PV, which inhibit SG formation through cleavage, would likely be unaffected by drugs that activate the stress response upstream of these cleaved factors. Another caveat to the potential use of these drugs is that SG formation may help the replication of certain viruses which induce SG to create a better environment for viral replication. The knowledge gained on the biology of SG and how it is influenced by viral infections will play a role in further characterizing innate responses to infection and how this system can be taken advantage of to curb viral infections.

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