



Strategies for Success. Viral Infections and Membraneless Organelles

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Specialty section:

This article was submitted to
Virus and Host,
a section of the journal
Frontiers in Cellular and Infection
Microbiology

Received: 28 May 2019

Accepted: 18 September 2019

Published: 11 October 2019

Citation:

Gaete-Argel A, Márquez CL,
Barriga GP, Soto-Rifo R and
Valiente-Echeverría F (2019)
Strategies for Success. Viral Infections
and Membraneless Organelles.
Front. Cell. Infect. Microbiol. 9:336.
doi: 10.3389/fcimb.2019.00336

Regulation of RNA homeostasis or “RNAstasis” is a central step in eukaryotic gene expression. From transcription to decay, cellular messenger RNAs (mRNAs) associate with specific proteins in order to regulate their entire cycle, including mRNA localization, translation and degradation, among others. The best characterized of such RNA-protein complexes, today named membraneless organelles, are Stress Granules (SGs) and Processing Bodies (PBs) which are involved in RNA storage and RNA decay/storage, respectively. Given that SGs and PBs are generally associated with repression of gene expression, viruses have evolved different mechanisms to counteract their assembly or to use them in their favor to successfully replicate within the host environment. In this review we summarize the current knowledge about the viral regulation of SGs and PBs, which could be a potential novel target for the development of broad-spectrum antiviral therapies.

Keywords: RNAstasis, RNA granules, membraneless organelles, stress granules, P-Bodies, anti-viral host immune response

INTRODUCTION

RNA plays key roles in all biological systems where RNAstasis is a *central processing unit* in the regulation of gene expression in eukaryotic cells (Sharp, 2009). RNAstasis include synthesis, modification, protection, storage, release, transportation and degradation of different types of RNA (mRNA, tRNA, rRNA, siRNA, miRNA, lncRNA, piRNA, snRNA, snoRNA, smRNA) and metabolic processes mediated by RNA-protein complexes called RNA granules. Depending on its localization, RNA granules are found in the nucleus, in the nucleolus, paraspeckles, nuclear speckles and Cajal bodies; or in the cytoplasm, as stress granules (SGs) and processing bodies (PBs). All are membraneless organelles (i.e., lack an enclosing membrane, MLOs) to allow for rapid exchange of components with the surrounding cellular environment (Fay and Anderson, 2018). MLOs contain a heterogeneous mixture of nucleic acids and proteins that present low-complexity regions (LCRs) and intrinsically disordered regions (IDRs) regulated by post-translational modifications (Ramaswami et al., 2013; Panas et al., 2016; Wheeler et al., 2016). MLO biogenesis has been shown to be via liquid-liquid phase separation (LLPS) process, supporting the high flexibility and quick adaptive responses to environmental stresses required for function (reviewed in Fay and Anderson, 2018).

After several rounds of translation, an mRNA undergoes degradation as a way of turnover. Indeed, it is suggested that mRNA degradation is tightly dependent on translation (Bicknell and Ricci, 2017).

However, under conditions of cellular stress, the cell responds by mounting a robust response causing the shutoff of protein synthesis in order to protect the mRNA so that translation can resume once the stress disappears. Repression of gene expression induces the assembly of RNA granules such as SGs and PBs, which are involved in mRNA triage and untranslated mRNA storage, respectively. By using single mRNA imaging in living human cells, it has been recently reported that a single mRNA can interact with both SGs and PBs (Wilbertz et al., 2018; Moon et al., 2019). However, while Wilbertz et al. showed that an mRNA preferably moves from a SG to a PB, Moon et al. showed a dynamic and bidirectional exchange of a single mRNA to multiple SGs and PBs (Wilbertz et al., 2018; Moon et al., 2019). Despite their distinctive organization and unique molecular markers, SGs and PBs share molecular components which could allow the dynamic shuttling of an mRNA between them (Kedersha et al., 2005).

Viral infections are a major trigger of cellular stress and, thus, viruses have evolved diverse mechanisms aimed to modulate host RNAstasis with a direct impact in the assembly of different RNA granules while counteracting mRNA decay machineries in order to ensure viral replication (Poblete-Durán et al., 2016; Toro-Ascuy et al., 2016). In this review, we provide an update on the current knowledge of the different strategies used by several virus families to modulate the RNA granules assembly/disassembly, specifically SGs and PBs, in order to promote a successful viral infection (see **Figure 1**).

VIRAL FAMILIES AND STRESS GRANULES

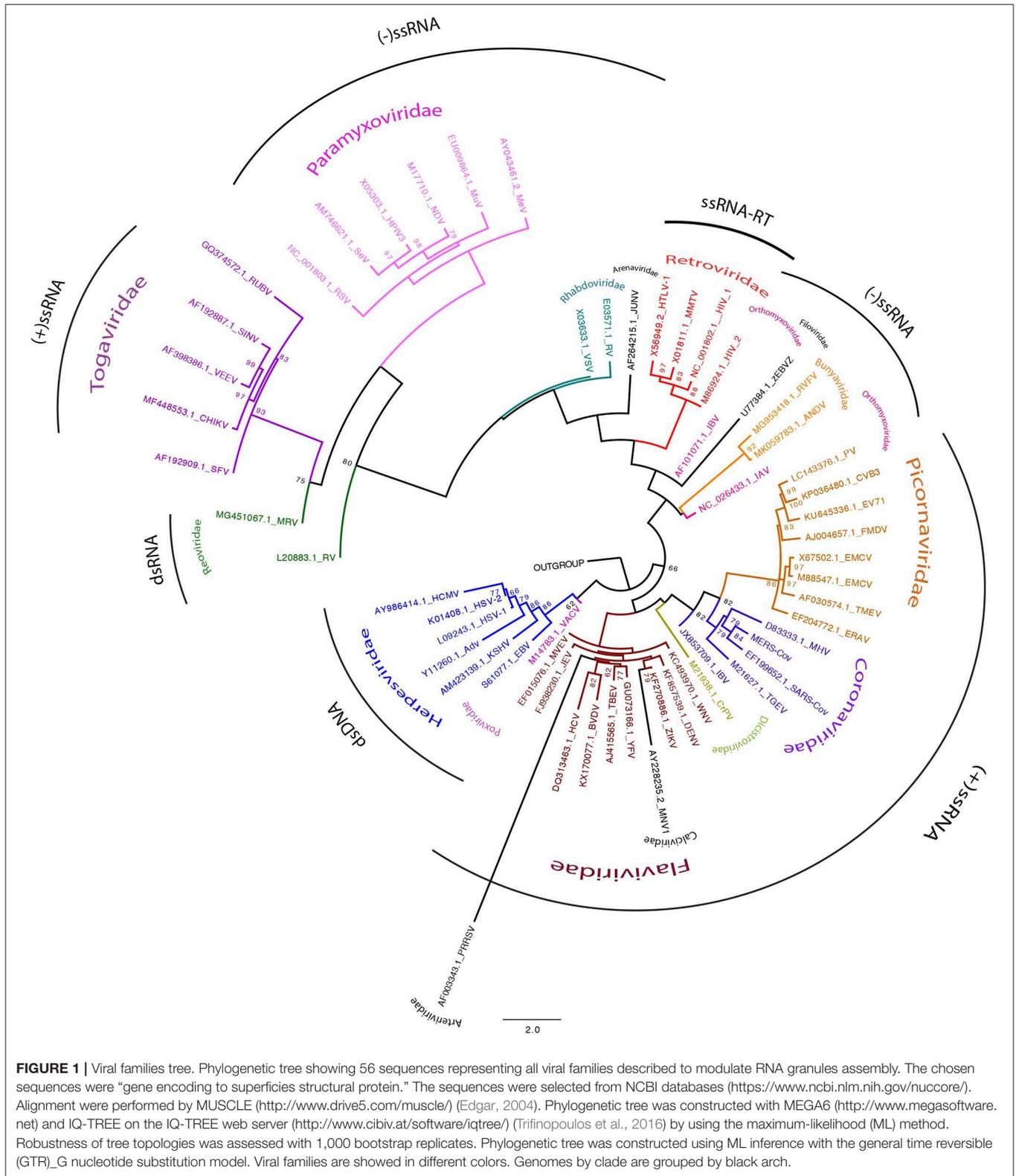
SGs are translationally silent membraneless organelles with a diameter between 0.1 and 4 μm . Canonical or *bona fide* SGs contain mRNA, RNA-binding proteins, and components of the 40S ribosomal subunit. Many proteins involved in SG assembly are RNA binding proteins that favor mRNA stability (TIA-1, TIAR, HuR), mRNA metabolism (G3BP-1, G3BP-2, DDX6, SMN, Staufen1, DHX36, Caprin1, ZBP1, HDAC6, ADAR), signaling proteins (mTOR, RACK1) and interferon-stimulated gene (ISG) products (PKR, ADAR1, RIG-I, RNase L, and OAS (reviewed in Poblete-Durán et al., 2016). Recently, Nunes et al. generated an open access electronic resource containing all SGs-recruited protein reported to date (available at <https://msgp.pt/>) (Nunes et al., 2019). Its assembly is typically a consequence of translation repression upon phosphorylation of the translation initiation factor eIF2 α by environmental stress such as heat shock, UV irradiation, oxidative stress, viral infection, and even upon treatment with several drugs (see **Table 1**). Most of these stresses are sensed by the eIF2 α kinases PKR, which is activated by double-stranded RNA during viral infection (Williams, 2001); PERK, which is activated upon accumulation of misfolded protein in the ER and during hypoxia (Harding et al., 2000); HRI, which is activated by oxidative stress and heme deprivation

(Han et al., 2001); and GCN2, which is activated by aminoacid deprivation and UV irradiation (Jiang and Wek, 2005). However, SGs can also be formed by inhibitors of translation that target other components of the translation machinery (**Table 1**) or by overexpression of SG-associated proteins such as TIA-1/TIAR or G3BP-1 (Kedersha et al., 1999; Tourrière et al., 2003). In addition to its role in mRNA triage, SGs have been described as signaling centers. Recruitment of signaling proteins to SGs allow the crosstalk between multiple stress cascades including translational control pathways, prevention of apoptosis and innate immune responses against viral infections (reviewed in Kedersha et al., 2011; Onomoto et al., 2014; Mahboubi and Stochaj, 2017).

Here, we summarize how viruses modulate SG accumulation in order to maintain viral protein synthesis and particles production.

Double-Stranded DNA (dsDNA) Viruses *Herpesviridae*

All members of the *Herpesviridae* family that have been studied prevent the accumulation of SGs. Herpes simplex virus type 1 (HSV-1) infection upregulates and relocalizes to the cytoplasm the SG components TTP, TIAR, and TIA-1 but does not induce SG assembly (Esclatine et al., 2004). The virion host shutoff (vhs) protein, an mRNA endonuclease, has been shown to be essential in SGs blockade as vhs-deficient HSV-1 (Δvhs) infected cells do trigger SG assembly (Esclatine et al., 2004; Dauber et al., 2011, 2016). HSV vhs is thought to facilitate viral mRNA translation throughout the viral cycle by reducing host mRNAs and preventing viral mRNA overload (Dauber et al., 2016). Δvhs -induced SGs accumulation correlates with increased PKR activation (Sciortino et al., 2013; Dauber et al., 2016; Burgess and Mohr, 2018), but while a group observed higher eIF2 α phosphorylation (Pasiaka et al., 2008; Burgess and Mohr, 2018), others did not (Dauber et al., 2011, 2016). This phenotype could be in part due the reduced levels of the late-expressed dsRNA binding protein Us11, that has been shown to block PKR activation (Mulvey et al., 2003; Dauber et al., 2011). Burgess and Mohr showed that dsRNA accumulates and partially localizes to Δvhs -induced SGs (Burgess and Mohr, 2018). Furthermore, they show that SGs are not assembled neither PKR is phosphorylated in Δvhs -infected cells upon treatment with ISRIB (see **Table 1**) or in absence of G3BP-1 or TIA-1. Based on these observations, the authors suggest that Δvhs -enhanced PKR activation is a consequence of SG assembly due to dsRNA accumulation (Burgess and Mohr, 2018). Interestingly, other HSV proteins have also been involved in SGs regulation, although it is not clear whether they all act cooperatively, or during different stages of the viral cycle. HSV-1 ICP27 has been shown to prevent formation of arsenite-induced SGs by inhibiting PKR and eIF2 α phosphorylation (Sharma et al., 2017). On the other hand, overexpression of HSV-1 ICP8 protein, a G3BP binding partner, blocks arsenite-induced SG assembly (Panas et al., 2015). Similar to HSV-1, SGs do not assemble during herpes simplex virus 2 (HSV-2) infection and its blockade is mediated by the vhs protein (Finnen et al., 2012; Dauber et al., 2014). HSV-2 vhs protein



has also been shown to shutoff protein synthesis by depleting mRNAs (Smith et al., 2000). Wild Type (WT) HSV-2 impairs arsenite-induced SGs despite increased eIF2 α phosphorylation,

but not pateamine (eIF2 α -independent)-induced SGs, indicating that vhs can disrupt or modify SGs independently of eIF2 α phosphorylation (Finnen et al., 2012). Further investigation

TABLE 1 | List of drugs/stressors used to induce or disassemble SGs and PBs.

Class	Drug/stressor	Effect	Mechanism	References
Translation inhibitors	Pateamine-A	Induces SG assembly	Interacts with eIF4A disrupting the eIF4F complex	Bordeleau et al., 2005; Kedersha et al., 2006
	Hippuristanol	Induces SG assembly	Inhibits eIF4A RNA binding activity	Bordeleau et al., 2006; Mazroui et al., 2006
	Cycloheximide	Disassembles both SGs and PBs	Inhibits eEF2-mediated translation elongation	Obrig et al., 1971; Mollet et al., 2008
	Selenite	Induces non-canonical SG assembly	Enhances 4EBP-1 binding to eIF4E, thus disrupting the eIF4F complex	Fujimura et al., 2012
	Sorbitol	Induces SG assembly	Causes osmotic stress, which enhances 4EBP-1 binding to eIF4E, thus disrupting the eIF4F complex	Patel et al., 2002
	Arsenite	Induces SG and PB assembly	Induces HRI-mediated eIF2 α phosphorylation*	McEwen et al., 2005
	Dithiothreitol (DTT)	Induces SG assembly	Induces PERK-mediated eIF2 α phosphorylation	Osowski and Urano, 2011; Dimasi et al., 2017
eIF2 α kinases Stressors	Heat-Shock	Induces SG assembly and inhibits PBs	Induces HRI-mediated eIF2 α phosphorylation	McEwen et al., 2005; Aulas et al., 2017
	Poly I:C	Induces SG assembly	Induces PKR-mediated eIF2 α phosphorylation	Weissbach and Scadden, 2012
	Bortezomib and MG132 (proteasome inhibitors)	Induce SG assembly	Induce HRI(Bortezomib)- and GCN2(MG132)-mediated eIF2 α phosphorylation	Mazroui et al., 2007; Fournier et al., 2010
eIF2 α modulators	Thapsigargin	Induces SG assembly	Induces PERK-mediated eIF2 α phosphorylation	Kimball et al., 2002
	ISRIB	Inhibit SG assembly	Prevents eIF2B inhibition, maintaining translation initiation despite eIF2 α phosphorylation	Sidrauski et al., 2015
Others	Salubrinal	Induces SG assembly	Blocks eIF2 α dephosphorylation	Boyce et al., 2005
	1,6-Hexanediol	Disassembles and induces PB and SG assembly	Disrupt weak hydrophobic interactions causing quick disassembly of granules that reappear after a few minutes**	Wheeler et al., 2016; Kroschwald et al., 2017
	Zn ⁺²	Stress- inducible second messenger	Induces reversible multimerization, phase separation and SG recruitment of TIA-1	Rayman et al., 2018

*Arsenite can also induce SG assembly independent of HRI. In *Drosophila*, which lacks HRI, induces the PEK eIF2 α kinase (Farny et al., 2009). In addition, Sharma et al. demonstrated that arsenite can also induce phosphorylation of PKR and SG assembly in HeLa and BCBL-1 cells (Sharma et al., 2017).

**It has been shown to also alter many other cellular structures (Wheeler et al., 2016).

revealed that (i) vhs localizes to SGs, (ii) vhs not only inhibits SG assembly but also disrupts pre-assembled SGs, and (iii) vhs endoribonuclease activity is required in SGs modulation (Finnen et al., 2016). Interestingly, TIA-1 was shown to egress before G3BP in the course of vhs-mediated SGs disassembly, which could be explained by the G3BP-enriched core SG structure (Jain et al., 2016; Niewidok et al., 2018). Based on these results, the authors proposed that HSV-2 vhs modify SGs by directly or indirectly degrading mRNA. Human cytomegalovirus (HCMV) inhibits the assembly of SGs but induces the unfolded protein response (UPR) (Isler et al., 2005a). Typically, this ER stress response leads to eIF2 α phosphorylation via PERK activation, but HCMV limits eIF2 α phosphorylation without diminishing PERK activation (Isler et al., 2005b). Marshall et al. showed that infection with HCMV lacking pTRS1 and pIRS1, dsRNA-binding proteins linked to PKR pathway inhibition, results in increased levels of eIF2 α phosphorylation and the reduction of viral protein synthesis (Marshall et al., 2009). Both proteins have identical amino-terminal regions and share 35% of similarity in their carboxy-terminal regions, suggesting that HCMV pTRS1 and pIRS1 have redundant roles in evading dsRNA-mediated

antiviral response. Ziehr et al. demonstrated that lack of both proteins also results in PKR activation and SG assembly, and that expression of either pTRS1 or pIRS1 is necessary and sufficient to prevent PKR activation, eIF2 α phosphorylation and SG assembly (Ziehr et al., 2016). Furthermore, pTRS1 PKR binding domain (PDB) was shown to be critical to accomplish those three phenotypes suggesting that the main mechanism of HCMV to inhibit SG assembly is through PKR antagonism. Strikingly, pTRS1 transfection interferes with arsenite-induced SG assembly in WT and PKR-depleted cells, but pTRS1- Δ PDB does not, suggesting that pTRS1 could also obstruct SG assembly promoted by other eIF2 α kinases and that its PDB is crucial for it. Kaposi's sarcoma-associated herpesvirus (KSHV) does not lead to SG accumulation via the viral protein ORF57 and SOX which are able to restrict arsenite-induced SG assembly independently (Sharma et al., 2017). ORF57, the HSV-1 ICP27 homologous, inhibits PKR/eIF2 α phosphorylation by directly interacting with PKR via its N-terminal dsRNA-binding domain, and with PACT via its two N-terminal RNA-binding motifs, thus obstructing PKR binding to both dsRNA and PACT. The mechanism and the spatiotemporal regulation of SG assembly

by the viral shutoff exonuclease SOX is unclear, but it might be related to its intrinsic RNA endonuclease activity similarly to HSV-2 vhs (Glaunsinger and Ganem, 2004; Sharma et al., 2017). Expression of Epstein–Barr virus (EBV) protein EB2, the counterpart of KSHV ORF57 and HSV-1 ICP27, does not abolish SG assembly, neither PKR/eIF2 α phosphorylation, indicating that this specific ability to regulate SGs is not conserved along herpesviruses (Sharma et al., 2017). Further research is necessary to define the effect of EBV on SG assembly.

Poxviridae

Unlike herpes viruses, Vaccinia virus (VACV), a member of *Poxviridae* family, exploits SG components to favor viral protein production (reviewed in Liem and Liu, 2016). VACV redistributes proteins from the host translation machinery and SGs, such as eIF4E, eIF4G, G3BP, and Caprin1 into viral replication factories (RFs) assembled in the cytoplasm of the host cell (Katsafanas and Moss, 2004, 2007). Notably, TIA-1 is not recruited into these replication foci (Walsh et al., 2008). How VACV redistributes each of these components remain unclear, but evidences have shown that VACV ssDNA-binding protein I3 associates and recruits eIF4G to ssDNA formed within the RFs (Zaborowska et al., 2012). Furthermore, it was shown that G3BP-1 and Caprin1 associate with nascent VACV DNA by mass spectrometry (Senkevich et al., 2017). Despite the disruption of canonical SGs for its own benefit, infection with the replication-defective VACV lacking E3L leads to the accumulation of granule-like structures around the RFs, named antiviral granules (AVGs), that arrest viral translation (Simpson-Holley et al., 2010). AVGs contain proteins that are typically found in SGs such as TIA-1, eIF3b, G3BP-1, and USP10, but they are not affected by cycloheximide, a drug that induce the disassembly of *bona fide* SGs (Simpson-Holley et al., 2010). AVG assembly requires eIF2 α phosphorylation via PKR activation (Simpson-Holley et al., 2010; Pham et al., 2016), process that is inhibited in presence of E3L (Chang et al., 1992). Furthermore, TIA-1 is an essential component of AVGs, as in its absence these antiviral granules are not formed even if PKR and eIF2 α are phosphorylated (Simpson-Holley et al., 2010). Interestingly, WT VACV infection also induces AVGs assembly that repress viral protein synthesis but to negligible levels (Rozelle et al., 2014). Recently, another mutant VACV lacking C7L/K1L was shown to induce AVG assembly (Liu and McFadden, 2014). AVGs accumulation was abolished and abortive infection was rescued in Δ C7L/K1L in SAMD9-depleted cells, suggesting that C7L/K1L antagonize SAMD9 host protein antiviral function. Even though SAMD9 localize to both Δ E3L and Δ C7L/K1L VACV induced-AVGs, infectivity neither AVG assembly is blocked with Δ E3L VACV in SAMD9-depleted cells, suggesting a different mode of organization of the granules induced by both mutants (Liu and McFadden, 2014). Δ C7L/K1L-dependent AVGs assembly is independent of eIF2 α phosphorylation, in contrast to Δ E3L AVG accumulation (Liu and McFadden, 2014). Viral mRNA was shown to colocalize with AVGs during Δ C7L/K1L VACV infection, thus limiting translation of viral proteins (Sivan et al., 2018), as well as dsRNA, TIA-1 and the viral protein E3L (Meng and Xiang,

2019). Despite of that, TIA-1 is not required for Δ C7L/K1L-mediated AVG assembly as it is on Δ E3L (Meng and Xiang, 2019). The role of each viral system, E3L and C7L/K1L, to prevent formation of AVGs in the context of viral infection remain to be studied.

Double-Stranded RNA (dsRNA) Viruses **Reoviridae**

Rotavirus replication, the prototypical member of the *Reoviridae* family, also occurs in viral replication factories and upon infection, synthesis of cellular proteins is reduced while viral protein production is maintained. Accumulation of viral dsRNA in the cytoplasm causes a persistent PKR-dependent eIF2 α phosphorylation, even when eIF2 α phosphorylation is not required for viral replication (Montero et al., 2008; Rojas et al., 2010). Despite that, rotavirus infection does not induce SG assembly; instead it changes the cellular localization of SG components (Montero et al., 2008). TIA-1 is relocated to the cytoplasm, eIF4E distributes more homogeneously in the cytoplasm, and PABP is translocated to the nucleus through the viral protein NSP3 (Montero et al., 2008). Recently, Dhillon et al. determined that rotavirus remodels SGs by excluding some of their proteins, such as G3BP-1, hnRNP A1, and ZBP1, and then recruits these atypical granules to viral replication factories (Dhillon and Rao, 2018; Dhillon et al., 2018). It will be of interest to understand how rotavirus selectively excludes these specific SG components. In contrast, uncoating of the mammalian orthoreovirus (MRV) during the early stage of infection leads to eIF2 α phosphorylation by the action of at least two eIF2 kinases, suggesting that MRV infection is a complex process that induces different types of stresses to the cell (Qin et al., 2009). Phosphorylation of eIF2 α triggers SG accumulation (Qin et al., 2009). MRV cores are then recruited into the assembled SGs, a step that depends on synthesis of viral mRNA. As the infection proceeds, assembled SGs are disrupted in order to allow efficient synthesis of viral proteins, despite the sustained levels of eIF2 α phosphorylation (Qin et al., 2011). Like rotavirus, MRV replication occurs in viral replication factories that grow in the perinuclear region (Rhim et al., 1962). The non-structural μ NS viral protein associates with σ NS, σ 2, μ 2, and λ 1 are recruited into viral replication factories. μ NS viral protein has been shown to localize with SGs, although is unable to independently prevent SGs accumulation (Carroll et al., 2014). Interestingly, the SG components G3BP-1, Caprin1, USP10, TIAR, TIA-1, and eIF3b were found to localize to the outer peripheries of viral replication factories (Choudhury et al., 2017). σ NS and μ NS were shown to be responsible for their redistribution as well as for disruption of the SG assembly. In addition, in the absence of G3BP-1 the other recruited SGs-associated protein, except for eIF3b, do not localize to RFs. The recruitment mode is thought to be as follows: Caprin1, USP10, TIAR, and TIA-1 interact with G3BP-1 which binds to σ NS via its RNA recognition (RRM) and an arginine/glycine-rich (RGG) motifs. Then, σ NS partner with μ NS for RF localization, carrying all the other proteins with it (Choudhury et al., 2017).

Positive-Sense Single Stranded RNA ((+) ssRNA) Viruses *Picornaviridae*

Members of the *Picornaviridae* family also modulate SGs accumulation during replication. Poliovirus (PV) regulates SGs in a time-dependent manner; at early times the 2A proteinase induces assembly of SGs (Mazroui et al., 2006; Chen et al., 2008) that are later disassembled by the 3C proteinase through G3BP-1 cleavage (White et al., 2007). Despite of *bona fide* SG disruption, atypical SGs (aSGs) that contain TIA-1 and viral RNA, but no eIF4G nor PABP, still accumulate later in the course of PV infection (Piotrowska et al., 2010; White and Lloyd, 2011). A similar temporal control of SG assembly is exhibited by Coxsackievirus B3 (CVB3) and Enterovirus 71 (EV71). CVB3 2A proteinase induces SG assembly as early as 3 h post infection (hpi) in an eIF2 α phosphorylation-independent manner (Wu et al., 2014; Zhai et al., 2018). It has been described that they have an antiviral role, inhibiting the biosynthesis of CVB3 (Zhai et al., 2018). However, at 6 hpi CVB3 induces the assembly of granules that do not contain G3BP-1 or eIF4G, likely because of G3BP-1 cleavage (Fung et al., 2013; Zhai et al., 2018). In the case of EV71, canonical SGs are assembled early during infection dependent on the PKR-eIF2 α pathway (Zhu et al., 2016), but are dispersed at late stages of infection (Yang et al., 2018b; Zhang et al., 2018). Yet, atypical SGs in which TIA-1, TIAR, Sam68, and viral RNA are persistently aggregated in an eIF2 α independent and cycloheximide-resistant manner remain during infection. Yang et al. showed that EV71 2A protease expression is enough for atypical SGs induction through the cleavage of eIF4GI and *bona fide* SGs blockage by abolishing eIF4GI-G3BP-1 interaction (Yang et al., 2018a,b). In contrast, Zhang et al. reported that EV71 3C protease alone is sufficient to inhibit canonical SGs accumulation during late stages of infection through G3BP-1 cleavage at amino acid Q326 (Zhang et al., 2018). Interestingly, cells infected with EV71-2AC110S (a cleavage-deficient 2A protease) do form canonical SGs in which viral RNA is aggregated, suggesting that EV71 blocks *bona fide* SGs but induce atypical SGs to facilitate viral translation by stalling only cellular mRNAs (Yang et al., 2018b; Zhang et al., 2018). Unlike already mentioned picornaviruses, encephalomyocarditis virus (EMCV) infection does not induce SG assembly at all, and cleavage of G3BP-1 is the mechanism for their disruption (Ng et al., 2013). On the other hand, the leader (L) protein of Theiler murine encephalomyelitis virus (TMEV) and mengovirus (a strain of EMCV) inhibit SG assembly without cleaving G3BP-1 (Borghese and Michiels, 2011; Langereis et al., 2013). A mutant mengovirus, in which the Zn-finger domain of L is disrupted, induces antiviral G3BP-1 aggregations in which Caprin-1 and PKR are recruited, resulting in PKR activation and viral replication inhibition (Langereis et al., 2013; Reineke et al., 2015). Foot and Mouth Disease Virus (FMDV) does not induce SG assembly despite strongly shutoff cap-dependent translation and G3BP-1 dephosphorylation at Ser-149 (Ye et al., 2018; Visser et al., 2019), suggesting that FMDV infection regulates the cellular stress response. In fact, G3BP-1, eIF4G, eIF3, and eIF2 α protein levels are downregulated and eIF4E-BP and PKR

are dephosphorylated during FMDV infection (Ye et al., 2018). Ye et al. showed that G3BP-1 cleavage by 3C protease impairs SG assembly (Ye et al., 2018) while Visser et al. argued that L protease catalytic activity is responsible for the impairment of SG assembly in infected cells, without affecting PKR signaling (White et al., 2007). In addition, Ye et al. reported that the 3C-induced cleavage of G3BP-1 inhibits the NF- κ B-dependent induction of antiviral immune responses (Ye et al., 2018). By using a reporter system, it has been shown that G3BP-1 negatively regulates viral translation by interacting with a structure located at domain 4 of the viral IRES (Galan et al., 2017). Furthermore, the G3BP-1 S149A substitution impairs the negative effect of G3BP-1 on IRES translation, suggesting that G3BP-1 is an antiviral protein whose activity depends on its phosphorylation (Ye et al., 2018). Instead, FMDV induces the nuclear-to-cytoplasm translocation of Sam68 via a proteolytic cleavage of its C-terminal domain mediated by 3C protease (Lawrence et al., 2012). Interestingly, Sam68 and TIA-1 colocalize in transient cytoplasmic granule-like structures in infected cells. Moreover, Sam68 interacts with FMDV IRES and Sam68 knockdown leads to a reduction in virus production, suggesting that Sam68 is a proviral factor (Lawrence et al., 2012; Rai et al., 2015). Similar to FMDV, Equine Rhinitis A virus (ERAV) infection also disrupts SG assembly via L-protease mediated cleavage of G3BP-1 and G3BP-2, suggesting that this is a conserved mechanism among aphtoviruses. However, despite G3BP-1 cleavage at multiple positions during FMDV and ERAV infections, the products differ in molecular weight, suggesting that they do not induce identical cleavages of G3BP-1 (Visser et al., 2019).

Togaviridae

Among viruses of *Togaviridae* family, Chikungunya virus (CHIKV) is the only member known to block SG assembly. G3BP-1 is sequestered by nsP3 in cytoplasmic foci (Fros et al., 2012) while G3BP-2 colocalizes with nsP2/3 in complexes different from viral replication factories (Scholte et al., 2015). Recently, it has been shown that dsRNA foci, nsP3-like granules and nsP1-coated structures are in close proximity, suggesting that CHIKV not only sequesters G3BP-1/-2 proteins in order to impair SGs assembly, but also to support viral replication (Remenyi et al., 2018). CHIKV dsRNA was shown to be undetectable in G3BP-1/-2 double knock-out (dKO) cells, indicating that G3BPs play key roles in RNA replication and formation of viral replication complexes (Kim et al., 2016). In contrast, Venezuelan Equine Encephalitis virus (VEEV) replication is not affected by G3BP-1/-2 dKO (Kim et al., 2016), but the SG-associated proteins FXR1, FXR2, and FMR1 have been shown to be essential factors for VEEV replication and protein production. Interestingly, VEEV infected cells contain both large and small plasma membrane-bound FXR-nsP3 complexes containing viral genomic RNA, suggesting a role of FXRs in viral replication and protection of viral genomic RNA from degradation during transport to the plasma membrane (Kim et al., 2016). Semliki Forest Virus (SFV) induces SG assembly early during infection in an eIF2 α phosphorylation-dependent manner (McInerney et al., 2005). Nevertheless, at late stages of infection nsP3

promotes SG disassembly by sequestering G3BP-1 to sites of viral replication, which correlates with an increase in viral RNA levels (McInerney et al., 2005; Panas et al., 2012). Consistently, infection with a non-G3BP-1 binding SFV promotes a persistent accumulation of SGs containing G3BP-1 and TIA-1, which correlates with an attenuation in viral infection (Panas et al., 2015). On the other hand, Sindbis virus (SINV)-derived vectors induce PKR activation and the subsequent assembly of SGs containing TIA-1, eIF4E, and eIF4G (Venticinque and Meruelo, 2010). Furthermore, viral nsP2, nsP3, and nsP4 colocalize with aggregates containing G3BP-1 (Frolova et al., 2006; Gorchakov et al., 2008; Cristea et al., 2010) while nsP3 also interacts with G3BP-2. In 2011, Mohankumar et al. revealed that SINV infection induces the phosphorylation of eIF2 α which correlates with a strong shutoff of *de novo* protein synthesis and 4E-BP1 dephosphorylation. Moreover, the authors demonstrated that SINV replication does not require the PI3K/Akt/mTOR pathway, and that later during infection, SINV suppresses Akt/mTOR activation in HEK cells (Mohankumar et al., 2011). Similar to CHIKV, G3BP-1/-2 dKO significantly reduce SINV replication rates and plaque size. However, FXR1/2 and FMR1 triple knock-out only induces a delay in viral particles production (Kim et al., 2016). Finally, it has been suggested that G3BP-1 plays a potential role in the encapsidation of Rubella virus (RUBV) due to the colocalization of RUBV genomic RNA, the non-structural viral protein P150 and G3BP-1 aggregates (Matthews and Frey, 2012).

Flaviviridae

West Nile virus (WNV), a member of the *Flaviviridae* family, was the first virus described to block SG assembly. The 3' stem loop in the (-) RNA, which is the site of initiation for nascent genome RNA synthesis, captures the SG components TIA-1 and TIAR, suggesting that they have a role in viral replication (Li et al., 2002). In addition, TIA-1 and TIAR colocalize with viral replication complexes containing dsRNA and NS3 viral protein in the perinuclear region (Emara and Brinton, 2007). Although WT WNV impedes SGs assembly, the chimeric WNV W956IC induces PKR-dependent SG assembly due to the high levels of viral RNA that are produced (Courtney et al., 2012). Remarkably, WNV inhibits arsenite, but not heat shock, or DTT-induced SG assembly. High levels of GSH (antioxidant) has been shown to counteract arsenite-induced SGs, as during WNV infection even low levels of PERK-mediated eIF2 α phosphorylation upregulate ATF4 and Nrf2, transcription factors that induce antioxidant gene expression (Basu et al., 2017). Similar to WNV, TIA-1, and TIAR colocalize with viral replication complexes containing dsRNA and NS3 in Dengue Virus type 2 (DENV-2) infected cells (Emara and Brinton, 2007). In addition, a quantitative mass spectrometry study revealed that DENV-2 RNA interacts with the SG components G3BP-1/2, Caprin1, and USP10 (Ward et al., 2011). It has been shown that DENV infection generates a non-coding subgenomic flaviviral RNA (sfRNA) that binds to G3BP-1/2 and Caprin1, impairing its ability to induce the translation of interferon Stimulated Genes (ISGs) mRNAs in response to DENV infection (Bidet et al., 2014). Recently, it has been described that Zika virus (ZIKV) infection blocks SG assembly (Amorim et al., 2017;

Basu et al., 2017; Hou et al., 2017; Bonenfant et al., 2019) despite a strongly induced translational shutoff and activation of both PKR- and UPR-induced phosphorylation of eIF2 α , suggesting that ZIKV impairs SG assembly downstream of eIF2 α phosphorylation (Hou et al., 2017). In addition, ZIKV infection impairs arsenite-, poly I:C and hippuristanol, but not DTT-, Pateamine A- and Selenite-induced SG assembly (Amorim et al., 2017; Hou et al., 2017; Bonenfant et al., 2019) without affecting levels of SG-nucleating proteins (Amorim et al., 2017; Bonenfant et al., 2019). Hou et al. showed that expression of ZIKV NS3, NS4, NS2B-3 or capsid protein are sufficient to inhibit SG assembly (Hou et al., 2017). Interestingly, during ZIKV infection the host proteins YB-1 and Ataxin-2 are redistributed to the nucleus, while HuR and TIA-1 are redistributed to the cytoplasm of infected cells (Bonenfant et al., 2019). Moreover, TIAR is partially redistributed to sites of viral replication in the perinuclear zone, as seen on its colocalization with NS1 and viral RNA (Amorim et al., 2017). Furthermore, G3BP-1 and HuR are isolated with replication complexes, but only G3BP-1 interacts with viral dsRNA (Hou et al., 2017; Bonenfant et al., 2019). G3BP-1, Caprin-1, TIAR, Ataxin-2 and YB-1 knockdown negatively affects virus production, while HuR and TIA-1 knockdown resulted in an increase of viral titers (Hou et al., 2017; Bonenfant et al., 2019). Specifically, G3BP-1 knockdown also decreases genomic RNA and viral protein levels, while HuR knockdown increases genomic RNA and protein level (Bonenfant et al., 2019). Together, these data suggest a possible proviral role of the SG components G3BP-1, Caprin-1, TIAR, Ataxin-2, and YB-1 in ZIKV replication (Hou et al., 2017; Bonenfant et al., 2019). Similar to ZIKV, Japanese encephalitis virus (JEV), Murray Valley Encephalitis Virus (MVEV) and Yellow Fever Virus (YFV) capsid-expressing cells showed a significantly impairment in hippuristanol-induced SG assembly (Hou et al., 2017). Specifically, it has been shown that JEV core protein blocks SG assembly through an interaction with Caprin-1, resulting in the recruitment of other SG components such as G3BP-1 and USP10 (Katoh et al., 2013). A JEV virus carrying a non Caprin-1-binding core protein is less pathogenic in mice and exhibits lower propagation *in vitro* than WT virus, suggesting that SGs blockade is crucial to facilitate viral replication (Katoh et al., 2013). Analogous to WNV and DENV, Tick-Borne Encephalitis virus (TBEV) sequesters TIA-1 and TIAR to viral replication factories (Albornoz et al., 2014). In particular, TIA-1 binds viral RNA and acts as a negative regulator of TBEV translation, suggesting that TIA-1 function is independent of SG assembly (Albornoz et al., 2014). In addition, TBEV infection induces eIF2 α -dependent SG assembly containing the canonical SGs markers G3BP-1, eIF3, and eIF4B (Albornoz et al., 2014). On the other hand, Bovine Viral Diarrhea virus (BVDV) impairs the assembly of arsenite-induced SGs and despite viral N-terminal protease (Npro) interaction with several SG components (such as YB-1, IGFBP2, DDX3, ILF2, and DXH9), this is not the mechanism by which BVDV blocks SG assembly (Jefferson et al., 2014). Hepatitis C virus (HCV) relocalizes G3BP-1, PABP1, ATX2, DDX3, TIA-1, and TIAR to viral replication factories in lipid droplets (LDs) (Ariumi et al., 2011; Garaigorta et al., 2012). In particular, DDX3 activates IKK α during HCV infection to induce LDs biogenesis

(Li et al., 2013). Importantly, Garaigorta et al. reported that G3BP-1, TIA-1, and TIAR are required for viral RNA and protein synthesis early during infection, while G3BP-1, DDX3, and TIA-1 play a role in viral particle assembly (Garaigorta et al., 2012; Pène et al., 2015; Valiente-Echeverría et al., 2015). In addition, they showed that HCV induces SG assembly in a PKR-dependent manner in order to impair the translation of antiviral ISGs (Garaigorta et al., 2012). Ruggieri et al. showed that HCV induces an oscillation between SG assembly and disassembly as a result of balance between dsRNA-dependent PKR activation with the subsequent phosphorylation of eIF2 α and the antagonist effect of GADD34-mediated dephosphorylation of eIF2 α (Ruggieri et al., 2012). This tight balance allows HCV to chronically infect cells without affecting cell survival (Ruggieri et al., 2012). In addition, two other SG components have been related to HCV replication: Stau1 and YB-1. Stau1 is involved in cellular mRNA transport, translation and decay, and negatively regulates the assembly of SGs (Thomas et al., 2009). Despite YB-1 being a general translational repressor, it regulates SG assembly by inducing G3BP-1 mRNA translation through its interaction with the 5'UTR of the mRNA (Somasekharan et al., 2015). In 2016, Dixit et al. showed that Stau1 interacts directly with PKR and NS5B, and that this interaction is required to inhibit PKR activation during HCV infection to allow viral RNA translation. In addition, the interaction of Stau1 with NS5B suggests a role of Stau1 in HCV replication, which is in accordance with a strong reduction in viral RNA and NS5A and NS5B protein levels in cells transfected with and Stau1-siRNA (Dixit et al., 2016). Moreover, Wang et al. demonstrated that YB-1 knockdown reduces the phosphorylation status of NS5A, which is crucial for the NS5A-mediated regulation of RNA replication and virus assembly (Wang et al., 2015). Also, YB-1 interacts with NS5A in an YB-1 phosphorylation-dependent manner and this interaction is crucial for NS5A protein stability during HCV infection. Interestingly, YB-1 is phosphorylated by Akt at serine 102 and is known that HCV infection and NS5A expression activate the PI3K/Akt signaling (Wang et al., 2015). Together, these observations could explain the oscillation of SG assembly/disassembly detected in HCV-infected cells (Ruggieri et al., 2012) and how SG assembly and SG components are necessary for HCV RNA replication, assembly and egress (Ariumi et al., 2011; Garaigorta et al., 2012; Pager et al., 2013).

Dicistroviridae

Cricket Paralysis Virus (CrPV) is the only described member of *Dicistroviridae* family that regulates SG assembly. CrPV 1A protein impairs the assembly of arsenite-, Pateamine A-, and heat shock-induced SGs containing Rox8 and Rin, *Drosophila* homologs of TIA-1 and G3BP-1 respectively, demonstrating that there is a conserved mechanism in insect and human cells (Khong and Jan, 2011; Khong et al., 2016). In addition, CrPV-induced inhibition of SG assembly is not due to a cleavage of Rox8 or Rin despite 3C proteinase sequestration in SGs (Khong and Jan, 2011).

Coronaviridae and Arteriviridae

Transmissible gastroenteritis virus (TGEV), a member of the *Coronaviridae* family, induces SG assembly later during infection

(Sola et al., 2011). The SGs component PTB binds to TGEV genomic and subgenomic RNA and colocalize with TGEV-induced aggregates containing TIA-1 and TIAR (Sola et al., 2011). In addition, Xue et al. described that PERK-mediated eIF2 α phosphorylation during TGEV infection is detrimental for viral replication due to the global translational repression induced by activation of the IFN pathway (Xue et al., 2018). On the other hand, Mouse Hepatitis Coronavirus (MHV) induces the aggregation of TIAR early during infection in an eIF2 α phosphorylation-dependent manner and, in contrast to TGEV, translational shutoff induced by MHV enhanced viral replication (Raaben et al., 2007). Moreover, MHV infection does not induce the expression of factors necessary to dephosphorylate eIF2 α such as CHOP and GADD34 (Bechill et al., 2008). MHV N protein strongly impairs the IFN-induced PKR signaling activation, suggesting a viral regulation of the cellular antiviral response (Ye et al., 2007). Recently, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was shown to impair SG assembly even when viral dsRNA alone activates PKR-mediated SG assembly, suggesting that the virus protects its viral dsRNA from PKR (Rabouw et al., 2016; Nakagawa et al., 2018). Rabouw et al. showed that viral protein p4a antagonizes PKR activity through its dsRNA-binding motif and inhibits partially arsenite-dependent SG assembly, suggesting that p4a suppresses PKR but no other pathways of the cellular stress response (Rabouw et al., 2016). In addition, MERS-CoV replication is significantly impaired in cells depleted of TIA-1 or G3BP-1/-2, suggesting a potential proviral role of these SG components (Nakagawa et al., 2018). Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) induces a strong inhibition of host protein synthesis mediated by the nsp1 viral protein, which interacts with the 40S ribosomal subunit, impairing 80S formation (Narayanan et al., 2008; Kamitani et al., 2009). In addition, SARS-CoV infection induces PKR-mediated eIF2 α phosphorylation, while GCN2 protein levels decreased in infected cells (Krahling et al., 2008). Finally, Infectious Bronchitis Coronavirus (IBV) induces PERK and eIF2 α phosphorylation at early times post infection, while induces GADD34 expression and the subsequent eIF2 α dephosphorylation at late stages of the course of infection in order to maintain viral protein synthesis (Wang X. et al., 2009; Liao et al., 2013). Interestingly, *IfnB* mRNA, but not IFN protein was detected in the supernatant of IBV infected cells, probably due to a 5b-mediated inhibition of general protein synthesis (Kint et al., 2016). However, although it has been described that SARS-CoV and IBV regulate eIF2 α phosphorylation in infected cells, it has not been evaluated whether it result in SG assembly or blockade. In contrast, it is known that Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), a member of the *Arteriviridae* family, induces canonical SG assembly mediated by PERK and eIF2 α phosphorylation in infected cells (Zhou et al., 2017).

Caliciviridae

Members of the *Caliciviridae* family block SG assembly by targeting G3BP-1. Although Feline Calicivirus (FCV) infection results in eIF2 α phosphorylation, viral 3C-like NS6 proteinase cleaves G3BP-1, thus impeding SG assembly in infected cells (Humoud et al., 2016). Similarly, Murine Norovirus 1 (MNV1)

induces a shutoff of global translation by triggering the phosphorylation of eIF4E and eIF2 α in a PKR-dependent manner, without inducing SG assembly (Royall et al., 2015; Brocard et al., 2018; Fritzlzar et al., 2019). Interestingly, MNV1 infected cells showed a redistribution of G3BP-1 to sites of viral replication closely to the nucleus, colocalizing with NS5 (Fritzlzar et al., 2019) or NS3 viral protein (Brocard et al., 2018). Together, these observations showed that MNV impairs SG assembly by sequestering G3BP-1, thus, uncoupling the cellular stress response (Brocard et al., 2018; Fritzlzar et al., 2019). Although Humoud et al. showed that MNV does not impair arsenite-induced SGs, recently Fritzlzar et al. demonstrated the opposite (Humoud et al., 2016; Fritzlzar et al., 2019).

Negative-Sense Single Stranded ((-) ssRNA) Viruses

Orthomyxoviridae

Influenza A virus (IAV) and Influenza B virus (IBV), members of the *Orthomyxoviridae* family, block SG assembly during infection. IAV disrupts SGs accumulation by expressing three different proteins: the host-shutoff protein polymerase-acidic protein-X (PA-X), the nucleoprotein (NP), and the non-structural protein 1 (NS1) (Khaperskyy et al., 2014). PA-X inhibits SG assembly in an eIF2 α -independent manner, and requires its endoribonuclease activity for this function (Khaperskyy et al., 2014). It causes nuclear relocalization of PABP1, a phenotype that has been observed with other viral host-shutoff proteins (Khaperskyy et al., 2014). In addition, it depletes poly(A) RNAs from the cytoplasm but promotes its accumulation in the nuclei (Khaperskyy et al., 2014). A recent publication demonstrates that PA-X selectivity degrades host RNAs by selecting transcripts that have undergone splicing, and that can interact with cellular proteins involved in RNA splicing (Gaucherand et al., 2019). NP can block arsenite-induced SGs accumulation in an eIF2 α -independent manner, but its effect depends on its expression levels (Khaperskyy et al., 2014). In contrast, NS-1-mediated inhibition of SG assembly depends on the PKR pathway; NS-1 binding to dsRNA inhibits PKR autophosphorylation and subsequent eIF2 α phosphorylation (Khaperskyy et al., 2011). Interestingly, the SGs-associated proteins RAP55, DDX3, and NF90 have been shown to interact with both NP and NS-1, which could represent the cell's attempt to inhibit IAV infection or most the virus hijacks these host proteins to block SG assembly (Wang P. et al., 2009; Mok et al., 2012; Li et al., 2016; Raman et al., 2016). NP and DDX3 are recruited to SGs during Δ NS1 IAV infection (Onomoto et al., 2012; Raman et al., 2016), but in presence of NS1 NP localizes to PBs instead, suggesting that NS1 is essential for NP escape from SGs (Mok et al., 2012). Normally NF90 leads to SG accumulation by directly binding and activating PKR, but in presence of IAV NS1, NF90 binds preferentially to it rather than PKR, suggesting that NS1 also suppress PKR activation by blocking NF90-PKR interaction (Wen et al., 2014; Li et al., 2016). Similarly, IBV requires NS1 in order to restrict SG assembly (Núñez et al., 2018). The vRNA sensor retinoic acid inducible gene I (RIG-I) is recruited to SGs and induces IFN response during Δ NS1 IAV

and IBV infections (Onomoto et al., 2012; Núñez et al., 2018). Furthermore, RIG-I was shown to associate with DDX6, which upon binding to vRNA stimulated RIG-I IFN induction (Núñez et al., 2018).

Arenaviridae

Infection with Junin virus (JUNV), a member of the *Arenaviridae* family, inhibits SG assembly in mock and arsenite-treated cells by impairing eIF2 α phosphorylation. To do so, the presence of either NP or glycoprotein precursor (GPC) is required, as they both block SGs accumulation when expressed individually in cells (Linero et al., 2011). Recently, JUNV NP was found to interact with PKR, G3BP-1, eIF2 α , hnRNP A1, and hnRNP K (King et al., 2017), as well as with DDX3 (Loureiro et al., 2018). Upon infection, PKR expression increases but is targeted to viral replication factories (RFs) together with NP, G3BP-1, dsRNA, PKR, phosphorylated PKR, RIG-I, and MDA-5 (King et al., 2017; Mateer et al., 2018). Despite the high levels of PKR activation, JUNV fails to induce eIF2 α phosphorylation, maybe due its sequestration to the RFs via NP (King et al., 2017). Lassa virus and lymphocytic choriomeningitis virus (LCMV) NPs also interact with G3BP-1, eIF2 α , and DDX3 (King et al., 2017; Loureiro et al., 2018). PKR interaction with LCMV NP occurs but weakly than with JUNV NP, which is reflected in the lack of PKR upregulation and colocalization with NP, and the increased eIF2 α phosphorylation level compared to JUNV infection (King et al., 2017).

Rhabdoviridae

The vesicular stomatitis virus (VSV), member of the *Rhabdoviridae* family, promotes eIF2 α phosphorylation and downregulates the synthesis of cellular proteins while maintaining viral production (Dinh et al., 2012). Under these conditions, it forms aSGs that contain PCBP2, TIA-1 and TIAR, but no eIF3 or eIF4A. VSV RNA, phosphoprotein (P) and NP are also part of these atypical SG-like structures, whose induction requires ongoing viral protein synthesis and viral replication (Dinh et al., 2012). Interestingly, assembly of aSGs and *bona fide* arsenite-induced SGs can occur simultaneously, revealing that VSV infection suppresses the accumulation of *bona fide* antiviral SGs and utilize SGs-associated components for its own benefit (Dinh et al., 2012). In contrast, Rabies virus (RABV) effectively replicate in cells that assemble SGs upon infection (Nikolic et al., 2016). The observed SGs contain G3BP-1, TIA-1 and PABP, and their accumulation is dependent on PKR-induced eIF2 α phosphorylation, suggesting that they are canonical SGs. Notably, PKR and TIA-1 depletion enhances viral replication, revealing that they have an antiviral effect but that is not strong enough to completely stop RABV infection. RABV-induced SGs locate adjacent to viral RFs. Interestingly, viral mRNA but no viral genomic RNA is transported from RFs to SGs, suggesting that RABV may be using SGs to modulate viral transcription and replication (Nikolic et al., 2016).

Paramyxoviridae

Respiratory Syncytial Virus (RSV), member of the *Paramyxoviridae* family, replicate in viral replication factories

(RFs) which have been observed to interact with SGs. However, seemingly contradictory findings have been reported for RSV. Lindquist et al. showed that RSV replication induces SG assembly in ~10–25% of the infected cells, and that they enhance RFs formation and viral replication (Lindquist et al., 2010, 2011). SGs accumulation requires PKR activation, which induces eIF2 α phosphorylation, however PKR depletion did not affect RSV replication (Lindquist et al., 2011). Contrastingly, Groskreutz et al. reported that RSV infection activates PKR but does not trigger eIF2 α phosphorylation due to PKR sequestration by the RSV NP (Groskreutz et al., 2010). Two other groups reported that RSV induce SG aggregation in ~1% (Hanley et al., 2010) and ~5% (Fricke et al., 2012) of the infected cells, revealing that, in general, RSV inhibits their assembly. Sequestration to RFs of the O-linked *N*-acetylglucosamine transferase (OGT), a factor involved in SGs regulation, and the presence of the 5' extragenic trailer sequence of the RSV genome have been associated with SGs suppression (Hanley et al., 2010; Fricke et al., 2012). Measles virus (MeV) infection does not induce SG assembly due to the PKR inhibitory effect of the viral accessory protein C (Okonski and Samuel, 2012). To block PKR autophosphorylation, MeV C protein requires the presence of the dsRNA binding protein and the SGs-component ADAR1, as WT MeV infection induce PKR activation and SGs accumulation in ADAR1 depleted cells (Toth et al., 2009; Li et al., 2012; Okonski and Samuel, 2012). Furthermore, infection with Δ C-MeV produces large amounts of dsRNA that activate PKR and induce SGs assembly, suggesting that the C protein may utilize ADAR1 to downregulate the viral dsRNA produced during replication (Pfaller et al., 2013). Both ADAR1 and C protein colocalize with SGs (Okonski and Samuel, 2012). Similar to RSV, Sendai virus (SeV) induces SGs accumulation in just a fraction of the cells (5–15%) and the 5' trailer region of its sequence has been implicated in SG assembly prevention via interaction with TIAR (Isemi et al., 2002). Like MeV, the SeV C protein is required to impair SG assembly in control and arsenite-treated cells, although C protein expression alone is not able to do so (Yoshida et al., 2015). Δ C-SeV assembled SGs contain RIG-I and unusual viral RNA species. Recently, the effect on SG assembly of three more paramyxoviruses have been studied. Newcastle disease virus (NDV) infection trigger the canonical SGs assembly to arrest host mRNAs and boost viral replication (Oh et al., 2016; Sun et al., 2017). SG assembly is dependent on PKR/eIF2 α phosphorylation and its suppression (by depleting TIA-1 or TIAR proteins) reduces viral protein synthesis but increases cellular protein synthesis (Sun et al., 2017). Accordingly, cellular mRNAs have been shown to be predominately recruited to SGs compared to viral mRNAs (Sun et al., 2017). Strikingly, RIG-I is also recruited to the assembled SGs, which induces IFN production as an antiviral response (Oh et al., 2016). Likewise, Mumps virus (MuV) infection promotes SG assembly dependent on PKR activation despite weak eIF2 α phosphorylation (Hashimoto et al., 2016). PKR, G3BP-1 and TIA-1 depletion reduces MeV-SGs and increased IFN response, but did not alter viral titers, suggesting that MuV replication occurs independently of the presence or absence of SGs. Conversely, Human Parainfluenza Virus Type

3 (HPIV3) infection leads to assembly of SGs that seem to have a poor antiviral role, as it is able to replicate in presence of SGs although viral protein expression and particle production is improved when SG assembly is constrained by knockdown of PKR, G3BP-1 or expression of a non-phosphorylatable eIF2 α (Hu et al., 2018). SG assembly is due eIF2 α PKR-dependent phosphorylation triggered by viral mRNAs, which can be shielded, and therefore block SGs assembly, by HPIV3 RFs (Hu et al., 2018).

Bunyaviridae

Since our last review (Poblete-Durán et al., 2016), no new reports have been published on how members of the *Bunyaviridae* family modulate SG assembly. Briefly, Rift Valley fever virus (RVFV) infection inhibit SG assembly despite attenuation of the Akt/mTOR signaling pathway which leads to the arrest of cap-dependent translation (Hopkins et al., 2015). It has been shown that non-structural protein from the S segment of Orthobunyaviruses, Hantaviruses and Phleboviruses (Kohl et al., 2003; Jaaskelainen et al., 2009), as well as glycoprotein Gn and the capsid N protein from Hantaviruses (Alff et al., 2006; Cimica et al., 2014; Matthys et al., 2014), inhibit IFN response.

Interestingly, the Andes Hantavirus (ANDV) N protein inhibits PKR dimerization, but this lack of activation does not stop protein translation (Wang and Mir, 2014). In contrast, RVFV infection promotes a protein translation shutoff due to PKR degradation by NSs protein (Habjan et al., 2009; Ikegami et al., 2009).

Filoviridae

Ebola virus (EBOV), member of the *Filoviridae* family, inhibits the assembly of SGs and instead sequesters the SGs-associated proteins eIF4G, eIF3, PABP, and G3BP-1, but no TIA-1 into granules within the viral replication factories (Nelson et al., 2016). These inclusion-bodies (IB) granules do not require eIF2 α phosphorylation, do not disassemble with cycloheximide, and do not block translation. Furthermore, arsenite, heat and hippuristanol can still induce *bona fide* SGs accumulation, suggesting that sequestration of SGs proteins in IB granules may be released upon stress. EBOV VP35 was found to be the protein that prevents the *bona fide* SG assembly late in infection, and its C-terminal domain is critical for this function (Le Sage et al., 2016). VP35-CTD contains an inhibition of interferon regulatory factor 3 (IRF3) domain that is responsible for blocking PKR activation during EBOV infection (Schumann et al., 2009). However, when expressed in sufficient high levels, VP35 can block arsenite-induced SGs without reducing the levels of eIF2 α phosphorylation, suggesting that VP35 suppress SG assembly by using an alternative way to PKR (Le Sage et al., 2016). VP35 can interact with several SG-associated proteins such as G3BP-1, eIF3, and eEF2 and it is targeted to viral replication factories, suggesting that it may be blocking SG assembly by relocating SG constituents (Le Sage et al., 2016; Nelson et al., 2016).

Single Strand RNA Retroviruses (ssRNA-RTs)

Retroviridae

Viruses belonging the *Retroviridae* family integrate its retrotranscribed (+)ssRNA into the host chromosomal DNA (Fields et al., 2013). The Human T-Lymphotropic Virus 1 (HTLV1) Tax protein blocks SG assembly by interacting with the SG components histone deacetylase 6 (HDAC6) (Legros et al., 2011) and USP10 (Takahashi et al., 2013). Similarly, the Human Immunodeficiency Virus Type I (HIV-1) also blocks SG assembly despite eIF2 α phosphorylation, through an interaction between Gag and the eukaryotic elongation factor 2 (eEF2) (Valiente-Echeverría et al., 2014; Poblete-Durán et al., 2016). HIV-1 Gag also disassembles pre-formed arsenite-induced SGs by interacting with G3BP-1 (Valiente-Echeverría et al., 2014) and selenite-induced atypical SGs by interacting with eIF4E (Cinti et al., 2016; Poblete-Durán et al., 2016). Notably, G3BP-1 was shown to act as a restriction factor that inhibits viral replication by interacting with HIV-1 genomic RNA (gRNA) in macrophages (Cobos Jiménez et al., 2015). Recently, Rao et al. described a novel HIV-1 NC-induced SGs containing G3BP-1, TIAR, eIF3, PABP, and poly(A) mRNAs that are no longer disassembled by Gag or CA (Rao et al., 2017). HIV-1 NC expression significantly increased eIF2 α phosphorylation, inhibiting protein synthesis and reducing viral particle production. In addition, NC was shown to interact with G3BP-1, TIAR, and Staufen1 even in absence of RNA. The inability of NC to assemble SGs in G3BP-1 depleted cells suggest that their interaction is required to promote NC-induced SG accumulation (Rao et al., 2017). The authors also showed that Staufen1 counteracts NC-induced PKR-dependent eIF2 α phosphorylation and translational shutoff (Rao et al., 2017). Interestingly, while HIV-1 impairs SGs assembly, the virus favors the assembly of Staufen1-containing HIV-1 dependent ribonucleoproteins (Abrahamyan et al., 2010). Indeed, it has been reported that HIV-1 is unable to dissociate or block arsenite-induced SG assembly in Staufen1 knock-out cells, suggesting that the recruitment of Staufen1 is crucial for HIV-1 SGs blockade. In addition, in absence of Staufen1 the HIV-1 genomic RNA colocalizes with TIAR in arsenite-induced SGs, which correlates with a significant reduction of Gag protein levels possibly due to the robust eIF2 α phosphorylation induced by HIV-1 infection (Rao et al., 2019b). Besides these data, Soto-Rifo et al. showed that DDX3, eIF4GI, and PABPC1 form a pre-translation initiation complex with the HIV-1 genomic RNA to promote viral translation (Soto-Rifo et al., 2014; Poblete-Durán et al., 2016). In contrast to HIV-1, HIV-2 infection does not block SG assembly and the viral genomic RNA recruits TIAR in a different type of RNA granules where it is suggested that the transition from translation to packaging occurs (Soto-Rifo et al., 2014). On another hand, Bann et al. showed that Mouse Mammary Tumor Virus (MMTV) Gag interacts and colocalizes with the SGs component YB-1 in small cytoplasmic foci in an RNA-dependent manner. Interestingly, these foci also contain viral RNA and are insensitive to cycloheximide treatment. It is suggested that YB-1 plays key roles in MMTV as YB-1

knockdown results in a significant reduction in viral particle production (Bann et al., 2014).

In summary, information about virus-host interaction mediated by membraneless organelles in order to ensure viral replication can be found summarized in **Table 2**.

VIRAL INFECTIONS AND PROCESSING BODIES

PBs are membraneless organelles and their diameter range between 150 and 340 nm (Cougot et al., 2012). PBs contain proteins involved in mRNA decapping machinery (Dcp1/2, LSm1-7, Edc3 proteins), scaffolding proteins (GW182, Ge-1/Hedls), deadenylation factors (Ccr1, Caf1, Not1), nonsense-mediated decay (NMD) proteins (SMG5-6-7, UPF1) and translation control factors (CPEB, eIF4E-T) (reviewed in Poblete-Durán et al., 2016). PBs are constitutively assembled in the cytoplasm of the cell, but their size and number increases upon cellular stress (Kedersha et al., 2005). Initially it was suggested that PBs were sites of mRNA decay, but recent evidences suggest that instead, P-bodies are sites of long-term mRNA storage and decapping enzymes (reviewed in Luo et al., 2018). Recent studies have shown that PBs participate in the storage of a selection of mRNAs; transcripts involved in regulatory processes are enriched while mRNAs that encode proteins that support basic cell functions are excluded (Hubstenberger et al., 2017; Standart and Weil, 2018).

Interestingly, viruses have been shown to modulate PB assembly by degrading and/or relocating PB-associated components, thus avoiding their accumulation. Here we summarize how viruses modulate PBs.

Double-Stranded DNA (dsDNA)Viruses

Adenoviridae

In order to accumulate late mRNAs, adenovirus decreases the number of PBs in the cell by relocating several PB components, such as DDX6, LSm1, Ge-1, Ago2, and Xrn1 to aggresomes, where proteins are inactivated or degraded (Greer et al., 2011). Aggresome formation is induced by the viral protein E4 11K, which was found to specifically bind DDX6, suggesting that this interaction may redistribute DDX6 (Greer et al., 2011). Recently, the PB-associated protein PatL1 was also shown to localize within aggresomes following E4 11K protein expression (Friedman and Karen, 2017).

Herpesviridae

In contrast to the aforementioned adenovirus, expression of PB-associated proteins and PBs accumulation increase upon HCMV infection, but viral mRNA is not targeted to them, suggesting that HCMV mRNAs escape translation repression (Seto et al., 2014). HCMV-induced PB assembly requires cellular but no viral RNA synthesis and was independent of the translational status of the cell (Seto et al., 2014). KSHV prevents PB assembly during latent and lytic infection thanks to the activation of the cytoskeletal regulator RhoA GTPase (RhoA) (Corcoran et al., 2012, 2015). How RhoA disperse PBs is unknown, but in both

TABLE 2 | Virus families that modulate SGs.

Genome	Virus family	Virus	SGs induction	SGs blockade	Mechanism	References
dsDNA	<i>Herpesviridae</i>	Herpes simplex Virus type 1 (HSV-1)	No	Yes	vhs is required for inhibition of SG assembly dependent on PKR	Esclatine et al., 2004; Dauber et al., 2011, 2016; Sciortino et al., 2013
					vhs-dependent SGs inhibition is independent on eIF2 α phosphorylation	Dauber et al., 2011, 2016
					vhs-dependent SG inhibition is dependent on eIF2 α phosphorylation, dsRNA partially localizes to SGs, and SG assembly activates PKR	Burgess and Mohr, 2018
					ICP27 inhibits phosphorylation of PKR/eIF2 α and blocks SG assembly	Sharma et al., 2017
		Herpes simplex virus type 2 (HSV-2)	No	Yes	HSV-2 inhibits SG assembly independent on eIF2 α phosphorylation	Finnen et al., 2012
					vhs is required for disruption of canonical and arsenite-induced SGs	Finnen et al., 2012
					vhs inhibit SG assembly and disrupt pre-assembled SGs, and its endoribonuclease activity is required	Finnen et al., 2016
		Cytomegalovirus (HCMV)	No	Yes	HCMV inhibits eIF2 α phosphorylation	Isler et al., 2005b
					HCMV inhibits SG assembly	Isler et al., 2005a
					Lack of viral proteins pIRS1 and pTRS1 increase levels of eIF2 α phosphorylation	Marshall et al., 2009
Kaposi's sarcoma-associated herpesvirus (KSHV)	No	Yes	ORF57 interacts with PKR inhibiting its binding to dsRNA and its activation, which impairs eIF2 α phosphorylation and SG assembly	Sharma et al., 2017		
			SOX inhibits arsenite-induced SG assembly	Sharma et al., 2017		
			EB2 overexpression does not abolish SG assembly neither PKR/eIF2 α phosphorylation	Sharma et al., 2017		
Epstein-Barr virus (EBV)	ND	ND				
<i>Poxviridae</i>	Vaccinia virus (VACV)	Yes (AVGs)	Yes	G3BP-1, Caprin 1, eIF4G, eIF4E, PABP are sequestered into RFs	Katsafanas and Moss, 2004	
				VACV lacking E3L induce AVGs which require TIA-1 expression	Simpson-Holley et al., 2010	
				Δ E3L induced AVGs requires eIF2 α phosphorylation	Pham et al., 2016	
				WT VACV spontaneously form AVGs but to negligible levels	Rozelle et al., 2014	
				Δ C7L/K1L VACV induce AVGs assembly dependent on SAMD9 host protein and independent of eIF2 α phosphorylation	Liu and McFadden, 2014	
				Viral mRNA is recruited to Δ C7L/K1L VACV induced AVGs	Sivan et al., 2018	
				TIA-1 is not required for Δ C7L/K1L-mediated AVG assembly	Meng and Xiang, 2019	
dsRNA	<i>Reoviridae</i>	Rotavirus	No	Yes	Rotavirus inhibits SG assembly independent on eIF2 α phosphorylation, but changes the localization of TIA-1, eIF4E, and PABP	Montero et al., 2008
		Mammalian orthoreovirus (MRV)	Yes (canonical)	Yes	Relocalizes ADAR1, Caprin1, CPEB, eIF2 α , 4EBP1, PKR, and Staufen1 to RFs, and selectively excludes G3BP-1 and ZBP1	Dhillon and Rao, 2018; Dhillon et al., 2018
					SGs are formed during the early stage of infection but disassembled in later stages independent on eIF2 α phosphorylation	Qin et al., 2009, 2011

(Continued)

TABLE 2 | Continued

Genome	Virus family	Virus	SGs induction	SGs blockade	Mechanism	References				
(+)	ssRNA	<i>Picornaviridae</i>	Poliovirus (PV)	Yes (canonical and atypical)	Yes	<p>μNS is recruited to SGs</p> <p>MRV relocalizes G3BP-1, Caprin1, USP10, TIAR, TIA-1, eIF3b to RFs via G3BP1-oNS-uNS interaction</p> <p>2A-protease mediated SGs assembly</p> <p>3C protease-mediated G3BP-1 cleavage</p> <p>Induces aggregates containing TIA-1 and viral RNA</p> <p>Cleavage of G3BP-1</p> <p>Cleavage of G3BP-1</p> <p>2A protease-mediated SGs assembly</p> <p>2A protease-mediated eIF4G cleavage</p> <p>Inhibition of SG assembly mediated by Leader protein (L)</p> <p>2A protease-mediated inhibition of SGs</p> <p>PKR-eIF2α phosphorylation- dependent SG assembly mediated by 2A protease</p> <p>Cleavage of eIF4GI mediated by 2A protease, abolishing eIF4GI and G3BP-1 interaction</p> <p>Cleavage of G3BP-1 mediated by 3C protease</p> <p>Shuts-off host cap-dependent translation mediated by eIF2α downregulation and PKR dephosphorylation</p> <p>Cleavage of G3BP-1 and Sam68 mediated by 3C protease</p> <p>Cleavage of G3BP-1 mediated by Leader protease</p>	<p>Carroll et al., 2014</p> <p>Núñez et al., 2018</p> <p>Mazroui et al., 2006</p> <p>White et al., 2007</p> <p>Piotrowska et al., 2010</p> <p>Ng et al., 2013</p> <p>Fung et al., 2013</p> <p>Zhai et al., 2018</p> <p>Wu et al., 2014</p> <p>Borghese and Michiels, 2011</p> <p>Zhu et al., 2016; Yang et al., 2018b</p> <p>Zhang et al., 2016, 2018; Zhu et al., 2016</p> <p>(Yang et al., 2018a,b)</p> <p>Zhang et al., 2018</p> <p>Ye et al., 2018</p> <p>Lawrence et al., 2012; Ye et al., 2018</p> <p>Visser et al., 2019</p> <p>Visser et al., 2019</p> <p>Langereis et al., 2013; Reineke et al., 2015</p> <p>McInerney et al., 2005</p> <p>Panas et al., 2012</p> <p>Panas et al., 2015</p> <p>Fros et al., 2012; Remenyi et al., 2018</p> <p>Scholte et al., 2015</p> <p>Matthews and Frey, 2012</p> <p>Kim et al., 2016</p> <p>Cristea et al., 2010</p> <p>Venticinque and Meruelo, 2010</p> <p>Kim et al., 2016</p>			
						Encephalomyocarditis virus (EMCV)	No	Yes	Cleavage of G3BP-1	Ng et al., 2013
						Coxsackievirus B3 CVB3	Yes (canonical and atypical)	Yes	Cleavage of G3BP-1	Fung et al., 2013
						Theiler's murine encephalomyelitis virus (TMEV)	No	Yes	Inhibition of SG assembly mediated by Leader protein (L)	Borghese and Michiels, 2011
						Enterovirus 71 (EV71)	Yes (canonical and atypical)	Yes	2A protease-mediated inhibition of SGs	Zhu et al., 2016; Yang et al., 2018b
						Foot-and-Mouth Disease Virus (FMDV)	No	Yes	PKR-eIF2 α phosphorylation- dependent SG assembly mediated by 2A protease	Zhang et al., 2016, 2018; Zhu et al., 2016
									Cleavage of eIF4GI mediated by 2A protease, abolishing eIF4GI and G3BP-1 interaction	(Yang et al., 2018a,b)
									Cleavage of G3BP-1 mediated by 3C protease	Zhang et al., 2018
									Shuts-off host cap-dependent translation mediated by eIF2 α downregulation and PKR dephosphorylation	Ye et al., 2018
									Cleavage of G3BP-1 and Sam68 mediated by 3C protease	Lawrence et al., 2012; Ye et al., 2018
									Cleavage of G3BP-1 mediated by Leader protease	Visser et al., 2019
									Cleavage of G3BP-1 and G3BP-2 by Leader protease	Visser et al., 2019
									Leader protein (L) inhibits SG assembly	Langereis et al., 2013; Reineke et al., 2015
									Induces eIF2 α phosphorylation	McInerney et al., 2005
<i>Togaviridae</i>	Semliki Forest Virus (SFV)	Yes (canonical)	Yes	nsP3 sequesters G3BP-1 and G3BP-2 into RFs	Panas et al., 2012					
				G3BP-1 binding by nsP3 is necessary for SGs blockage	Panas et al., 2015					
	Chikungunya virus (CHIKV)	No	Yes	Nsp3 sequesters G3BP-1 to RFs	Fros et al., 2012; Remenyi et al., 2018					
	Rubella virus (RUBV)	Yes	No	G3BP-2 colocalizes with nsP2/nsP3 complexes	Scholte et al., 2015					
	Venezuelan equine encephalitis virus (VEEV)	ND	ND	Accumulation of G3BP-1	Matthews and Frey, 2012					
			nsP3 interacts with FXRs to facilitate viral RFs formation	Kim et al., 2016						
			Nsp4 interacts with G3BP-1	Cristea et al., 2010						
			Induces PKR-dependent SGs assembly	Venticinque and Meruelo, 2010						
			Nsp3 protein interacts with G3BP-1 and G3BP-2	Kim et al., 2016						

(Continued)

TABLE 2 | Continued

Genome	Virus family	Virus	SGs induction	SGs blockade	Mechanism	References				
Flaviviridae	West Nile Virus (WNV)	West Nile Virus (WNV)	No	Yes	Viral RNA captures TIA-1 and TIAR Increased GSH levels inhibit arsenite-induced SGs	Li et al., 2002 Basu et al., 2017				
						Dengue Virus (DENV)	No	Yes	Viral RNA colocalizes with TIA-1 and TIAR 3'UTR interacts with G3BP-1, G3BP-2, Caprin 1 and USP1	Emara and Brinton, 2007 Ward et al., 2011
										Zika Virus (ZIKV)
	Yellow Fever Virus (YFV)	ND	Yes	Ectopically expressed capsid protein blocks hippuristanol-induced SGs	Hou et al., 2017					
					Murray Valley Encephalitis Virus (MVEV)	ND	Yes	Ectopically expressed capsid protein blocks hippuristanol-induced SGs	Hou et al., 2017	
	Tick-borne encephalitis virus (TBEV)	Yes (canonical)	No	Induces eIF2 α phosphorylation Sequesters TIA-1 and TIAR to RFs					Albornoz et al., 2014 Albornoz et al., 2014	
					Japanese encephalitis virus (JEV)	No	Yes	Core protein interacts with Caprin 1 Ectopically expressed capsid protein blocks hippuristanol-induced SGs	Katoh et al., 2013 Hou et al., 2017	
	Bovine viral diarrhea virus (BVDV)	No	Yes	Impairs arsenite-induced SGs assembly					Jefferson et al., 2014	
					Hepatitis C virus (HCV)	Yes	Yes	G3BP-1, Ataxin-2, PABP1, DDX3, TIA-1, and TIAR are recruited to lipid droplets Induces SGs dependent on PKR and IFN GADD34-mediated SGs disassembly DDX3 binds viral 3'UTR DDX3 and G3BP-1 localize with HCV core protein Staufen 1 inhibits PKR activation	Ariumi et al., 2011; Garaigorta et al., 2012 Garaigorta et al., 2012 Ruggieri et al., 2012 Li et al., 2013 Pène et al., 2015 Dixit et al., 2016	
	Dicrostoviridae	Cricket paralysis virus (CrPV)	No	Yes					3C protease is sequestered to SGs CrPV-1A protein disrupts Pateamine A, arsenite and heat shock-induced SGs assembly	Khong and Jan, 2011 Khong et al., 2016
Coronaviridae					Mouse hepatitis coronavirus (MHV)	Yes	No	Induces eIF2 α phosphorylation N protein impairs PKR and eIF2 α phosphorylation during IFN treatment		Raaben et al., 2007; Bechill et al., 2008 Ye et al., 2007
	Transmissible gastroenteritis virus (TGEV)	Yes	No	PTB localization in SGs correlates with an increase in viral replication Induces PERK-dependent eIF2 α phosphorylation					Sola et al., 2011 Xue et al., 2018	
					Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	No	Yes	4a protein inhibits PKR-dependent SG assembly by binding and sequestering dsRNAs from PKR	Rabouw et al., 2016; Nakagawa et al., 2018	
	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	ND	ND	Nsp1 induces translational shutoff by impairing 80S formation Induces PKR and eIF2 α phosphorylation					Narayanan et al., 2008; Kamitani et al., 2009 Krahling et al., 2008	
					Infectious Bronchitis Coronavirus (IBV)	ND	ND	Induces PKR and eIF2 α phosphorylation at early stages of infection and inhibits eIF2 α phosphorylation at later stages Viral 5b protein induces host translational shutoff	Wang X. et al., 2009; Liao et al., 2013 Kint et al., 2016	

(Continued)

TABLE 2 | Continued

Genome	Virus family	Virus	SGs induction	SGs blockade	Mechanism	References
	<i>Arteriviridae</i>	Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)	Yes (canonical)	ND	Induces PERK-dependent eIF2 α phosphorylation and subsequent SGs assembly	Zhou et al., 2017
		Feline Calicivirus (FCV)	No	Yes	Induces Mnk1-mediated eIF4E phosphorylation Induces PKR and eIF2 α phosphorylation, but translation repression is PKR-independent G3BP-1 is sequestered to RFs even in presence of arsenite treatment	Royall et al., 2015 Fritzlar et al., 2019 Fritzlar et al., 2019
(-)ssRNA	<i>Orthomyxoviridae</i>	Influenza A virus (IAV)	No	Yes	G3BP-1 colocalizes with Nsp3 in a perinuclear zone but not in presence of arsenite treatment NS6-mediated G3BP-1 cleavage NS1 restrict SG assembly dependent on eIF2 α while NP and PA-X block SG assembly in an eIF2 α -independent manner PA-X requires its endoribonuclease activity to inhibit SGs, and relocalizes PABP1 to the nucleus PA-X selectively degrades host spliced RNAs NS-1 inhibits PKR activation by binding to dsRNA NS1 interacts with RAP55 and its RNA and PKR binding sites are required for the interaction and to inhibit SGs NS1 and NP interact with DDX3 NP and RIG-I are recruited to SGs on Δ NS1 IAV infection, and IAV genomic RNA is sufficient to form SGs	Humoud et al., 2016 Khapersky et al., 2014 Khapersky et al., 2014 Gaucherand et al., 2019 Khapersky et al., 2011 Mok et al., 2012 Raman et al., 2016 Onomoto et al., 2012
		Influenza B virus (IBV)	No	Yes	NS1 interacts with NF90 and restricts its binding to PKR. The NS1 RNA-binding domain and the NF90 double-stranded RNA binding domain are required NF90 binds NP independently of RNA binding NS1 is required to inhibit SG assembly. RIG-I and DDX6 interact and colocalize to Δ NS1-induced SGs	Wen et al., 2014; Li et al., 2016 Wang P. et al., 2009 Núñez et al., 2018
	<i>Arenaviridae</i>	Junin Virus (JUNV)	No	Yes	NP and GPC individually impair arsenite-induced SGs by inhibiting eIF2 α phosphorylation NP interacts with G3BP-1, PKR, hnRNP A1, and hnRNP K, G3BP-1 and eIF2 α . NP sequesters PKR into RFs NP interacts with DDX3 dsRNA activates PKR and colocalizes with RFs	Linero et al., 2011 King et al., 2017 Loureiro et al., 2018 Mateer et al., 2018
	<i>Rhabdoviridae</i>	Vesicular stomatitis virus (VSV)	Yes (atypical)	Yes	Inhibit canonical SGs but induces SGs-like structures containing PCBP2, TIA1, TIAR, and viral RNA, P and NP proteins	Dinh et al., 2012
		Rabies virus	Yes (canonical)	No	SG assembly is dependent on PKR and they locate close to RFs. Viral mRNA is transported to RFs	Nikolic et al., 2016
	<i>Paramyxoviridae</i>	Respiratory Syncytial Virus (RSV)	Yes (canonical)	Yes	10–25% of infected cells form SGs dependent on PKR Just 1% of infected cells form SGs. The 5'trailer region of the RSV genome is required to inhibit SGs Just 5% of infected cells form SGs. Sequestration of OGT into RFs suppresses SGs accumulation	Lindquist et al., 2010, 2011 Hanley et al., 2010 Fricke et al., 2012
		Measles virus (MeV)	No	Yes	Viral C protein inhibits SG assembly by blocking PKR activation but requires the presence of ADAR1	Okonski and Samuel, 2012

(Continued)

TABLE 2 | Continued

Genome	Virus family	Virus	SGs induction	SGs blockade	Mechanism	References
		Sendai virus (SeV)	Yes (canonical)	Yes	MeV C protein reduces the dsRNA in the cytoplasm to inhibit PKR activation 5–15% of infected cells form SGs. The trailer RNA region captures TIAR and inhibit SGs accumulation	Pfaller et al., 2013 Iseki et al., 2002
		Newcastle disease virus (NDV)	Yes (canonical)	No	Viral C protein is required to inhibit SG assembly NDV replication induces canonical SGs which contain vRNA(+) and RIG-I SG assembly is dependent on PKR/eIF2 α pathway. SGs contain cellular mRNA but no viral mRNA	Yoshida et al., 2015 Oh et al., 2016 Sun et al., 2017
		Mumps virus (MuV)	Yes (canonical)	No	SG assembly is dependent on PKR. MuV replicates independently of the presence or absence of SGs	Hashimoto et al., 2016
		Human parainfluenza virus type 3 (HPIV3)	Yes	No	PKR-dependent SGs are induced by viral mRNA. SGs have an inhibitory role in HPIV3 replication.	Hu et al., 2018
	<i>Bunyaviridae</i>	Rift Valley fever virus (RVFV)	Yes	Yes	Attenuate Atk/mTOR signaling	Hopkins et al., 2015
		Andes hantavirus (ANDV)	ND	Yes	N protein inhibits PKR activation	Wang and Mir, 2014
	<i>Filoviridae</i>	Ebola virus	Yes (IB granules)	Yes	Ebola inhibits canonical SGs but form IB granules within RFs that contain eIF4G, eIF3, PABP, and G3BP-1, but no TIA-1 VP35 inhibit canonical and stress-induced SGs, and its C-terminal domain is required. VP35 interacts with G3BP-1, eIF3, and eEF2	Nelson et al., 2016 Le Sage et al., 2016
ssRNA-RT	<i>Retroviridae</i>	Human T-cell Leukemia virus (HTLV-1)	No	Yes	Tax interacts with HDAC6 and USP10	Legros et al., 2011; Takahashi et al., 2013
		Human immunodeficiency virus type 1 (HIV-1)	No	Yes	Staufen 1 and Gag-mediated blockade of SGs assembly Gag interacts with eEF2 to block SGs assembly	Abrahamyan et al., 2010 Valiente-Echeverría et al., 2014
					G3BP-1 interact with Gag to disassembly preformed SGs gRNA promote pre-translation initiation complex assembly	Valiente-Echeverría et al., 2014 Soto-Rifo et al., 2014
					Gag interacts with eIF4E to promote disassembly of SGs	Cinti et al., 2016
					Ectopically expressed NC protein induces eIF2 α phosphorylation and interacts with SGs proteins. gRNA and TIAR colocalizes in SGs	Rao et al., 2017 Soto-Rifo et al., 2014
		Human immunodeficiency virus type 2(HIV-2)	Yes	No		
		Mouse Mammary Tumor Virus (MMTV)	ND	ND	YB-1 interacts with Gag and gRNA in cytoplasmic foci	Bann et al., 2014

cases its activated by the p38/MK2 pathway, which is triggered by the viral gene G-protein-coupled receptor (vGPCR) during lytic infection, and by the viral kaposin B (KapB) protein during latency (Corcoran et al., 2012, 2015). Furthermore, on both cycles PBs inhibition causes stabilization of AU-rich containing RNAs, a *cis-acting* RNA element usually present in mRNAs coding cytokines, growth factors and proto-oncogenes, increasing their protein synthesis during infection (Corcoran et al., 2012, 2015).

Double-Stranded RNA (dsRNA) Viruses *Reoviridae*

Similarly, rotavirus has also been shown to suppress PB assembly (Montero et al., 2008; Bhowmick et al., 2015). Upon infection, it reduces the cytosolic levels of Xrn1, Pan3, and Dcp1a, but

no GW182 in a time-dependent manner (Bhowmick et al., 2015). Furthermore, it has been shown that rotavirus infection induces the relocalization of Xrn1, Dcp1a, and PABP to the nucleus (Montero et al., 2008; Bhowmick et al., 2015), and to sequester most of the PB components into RFs, with the exception of DDX6, Edc4, and Pan3 (Dhillon and Rao, 2018; Dhillon et al., 2018), and to accelerate Pan3 decay by the NSP1 protein (Bhowmick et al., 2015).

Positive-Sense Single Stranded RNA ((+) ssRNA) Viruses *Flaviviridae*

The relationship between (+)ssRNA and PB components has been extensively studied. Members of the Flavivirus genus of

the *Flaviviridae* family generates a subgenomic flavivirus RNA (sRNA) as a product of genomic RNA incomplete degradation by the exonuclease Xrn1 (Pijlman et al., 2008; Silva et al., 2010). In that process, Xrn1 stalls on highly structured sequences in the 3' UTR, thus inhibiting Xrn1 activity and resulting in the accumulation of uncapped cellular mRNAs (Pijlman et al., 2008; Moon et al., 2012). Interestingly, sRNA colocalizes with Xrn1 in PBs and is essential for viral-mediated cytopathogenesis (Pijlman et al., 2008). The flavivirus WNV reduces PB assembly during the course of infection through the sequestration of several PB components such as LSm1, GW182, Xrn1, DDX3, and DDX6 to viral replication factories (RFs) (Chahar et al., 2013). Similarly, DENV infection reduces PBs accumulation through an interaction of DENV 3'UTR with DDX6 (Ward et al., 2011). In addition, it has been shown that Dcp1b colocalizes with viral dsRNA, suggesting that DENV RNA replication occurs within PBs (Dong et al., 2015). LSm1, another PBs component, interacts with DENV RNA both *in vitro* and *in vivo* during DENV-2 infection, colocalizing with sites of viral replication (Dong et al., 2015). Moreover, downregulation of LSm1 negatively affects viral RNA accumulation and particle production, suggesting that LSm1 plays key roles in the early stages of the viral replicative cycle, such as translation and replication (Dong et al., 2015). In 2016 Balinsky et al. showed that NS4A and NS3 interact with IRAV, which is a constituent of PBs and is induced by DENV infection in an interferon-dependent manner. Interestingly, IRAV is relocalized to viral RFs in HEK-293T cells and in monocyte-derived macrophages (Balinsky et al., 2017). MOV10 is also relocalized to viral RFs, as shown by its colocalization with NS3. Both IRAV and MOV10 are restriction factors for DENV, as viral replication is significantly enhanced in KO and KD cells, respectively (Balinsky et al., 2017). ZIKV infection does not affect the morphology, localization or number of PBs per cell (Hou et al., 2017), however both DDX6 and DGCR8 are upregulated in ZIKV-infected neurospheres (Garcez et al., 2017). Interestingly, nonsense-mediated mRNA decay (NMD) transcripts are stabilized in ZIKV-infected cells, suggesting that NMD pathway is impaired in infected cells. In addition, ZIKV capsid interacts with several NMD components, including nuclear Upf1, which is targeted for proteasomal degradation (Fontaine et al., 2018). Downregulation of Upf1 prior to infection significantly increases RNA viral levels and consequently viral production, suggesting that Upf1 regulates early stages of ZIKV infection (Fontaine et al., 2018). Similar to the other flavivirus mentioned above, HCV induces the relocalization of several PB components such as DDX6, LSm1, Xrn1, PatL1, Ago2, Dicer, and DDX3 to sites of viral replication in lipid droplets (Ariumi et al., 2011; Berezchna et al., 2011; Pager et al., 2013) in order to promote viral replication (Ariumi et al., 2007, 2011; Berezchna et al., 2011; Pager et al., 2013). In particular, the decapping activators DDX6, LSm1, and PatL1 are crucial for the transition from translation to replication of HCV RNA (Scheller et al., 2009; Jangra et al., 2010). Although PB constituents play key roles during HCV infection, the presence of PBs is not necessary for efficient viral replication (Berezchna et al., 2011; Pérez-Vilaró et al., 2012). Analysis of liver biopsies from HCV-infected patients confirmed that HCV decreases

the number of PB *in vivo* independent of the viral genotype, the inflammation status of the sample donor or whether the infection is chronic or recent. Interestingly and contrary to previous reports, DDX6 was shown to not be recruited to sites of viral replication at lipid droplets (Pérez-Vilar et al., 2015), although its role in HCV replication in patient samples remains to be elucidated. This article by Pérez-Vilaró et al. is the first evidence and confirmation of a direct relationship between a viral-induced pathogenesis and PB modulation. Furthermore, they reported differences in PB composition since DDX6 do not colocalize with Dcp1 in human hepatocytes *in vivo*, highlighting the potential variations between cell line-based experiments and analysis of human or animal models (Pérez-Vilar et al., 2015). Although HCV and BVDV do not generate a sRNA from their 3'UTR as other flavivirus such as DENV, Moon et al. showed that Xrn1 stalls while attempting to degrade the 5'UTR of both HCV and BVDV, thus Xrn1 activity is repressed. This dysregulation causes a stabilization of mRNAs encoding proteins involved in innate immune responses and transcription factors, which have short half-life in uninfected cells (Moon et al., 2015). In addition, they suggest that HCV-mediated Xrn1 repression induces a feedback mechanism that prevents the initial steps of 5'-3' decay, such as deadenylation and decapping (Moon et al., 2015).

Picornaviridae

The picornaviruses PV and CVB3 3C proteases cleave Dcp1a and target Xrn1 and Pan3 for proteasomal degradation, thus resulting in the total disruption of PBs (Dougherty et al., 2011; Poblete-Durán et al., 2016). In addition, CVB3 2A protease relocalizes AUF1 (also known as hnRNP D) from the nucleus to the cytoplasm of infected cells and 3C protease cleaves AUF1 (Wong et al., 2013). Moreover, AUF1 knockdown significantly enhances viral RNA abundance, suggesting that AUF1 is a restriction factor for CVB3 replication. Interestingly, AUF1 binds to the 3'UTR of viral genome containing AU-rich sequences and likely targets it for degradation, thus CVB3 counteracts AUF1-induced degradation of the viral RNA genome by targeting AUF1 for degradation (Wong et al., 2013). In addition, it has been reported that MOV10 is a restriction factor for EMCV and CVB3 replication. Thus, both EMCV and CVB3 viral 3C protease induces the cleavage of MOV10 to counteract its antiviral activity (Cuevas et al., 2016). Enterovirus 71 (EV71) increases the number of PBs at early stages but disrupt PBs at late stages of infection (Wang et al., 2016; Zhu et al., 2016; Yang et al., 2018b). In addition, EV71 2C protease reduces the expression of APOBEC3G (A3G) by targeting to degradation via the autophagy-lysosome pathway. Surprisingly, A3G antiviral activity does not depend on its cytidine deaminase activity but restricts viral replication by binding to the viral 5'UTR thus displacing PCBP1, which is essential for the replication of picornaviruses such EV71 (Li et al., 2018). In contrast, MOV10 is a positive regulator of EV71 replication through its binding to a cloverleaf-like structure and the IRES of viral RNA, facilitating replication and viral protein synthesis (Wang et al., 2016). Upon EV71 infection MOV10 co-localized with PBs and it is suggested that

MOV10 relocalization is a host response to impair viral MOV10 recruitment (Wang et al., 2016).

Dicistroviridae and Togaviridae

CrPV, a member of the *Dicistroviridae* family, selectively disrupts GW182/Dcp1 but not Ago1/Ago2 aggregates, suggesting that they play differential roles during infection (Khong and Jan, 2011), while that RNAs of SINV, a virus that belong to the *Togaviridae* family, interact with HuR in order to stabilize and avoid the cellular mRNA decay machinery (Sokoloski et al., 2010). It was reported that Upf1 knockdown increases SINV and Semliki Forest Virus (SFV) RNA replication. Thus, Upf1 has an antiviral activity, probably by promoting viral RNA degradation. In addition, Upf1-mediated inhibition of viral replication also involved other NMD components, such as Smg5 and Smg7 (Balistreri et al., 2014). On other hand, the coronavirus MHV induces the degradation of several cellular mRNAs encoding translation-related factors with a concomitant translational shut off and increase in the number of PBs per cell (Raaben et al., 2007). The mechanism behind MHV-induced regulation of mRNA decay is still unknown. Similarly, SARS-CoV Nsp1 promotes mRNA downregulation as a consequence of global mRNA degradation in order to maximize viral RNA translation (Huang et al., 2011). In contrast, TGEV infection decreases significantly the number of PBs by an unknown mechanism (Sola et al., 2011).

Negative-Sense Single Stranded ((-) ssRNA) Viruses

Orthomyxoviridae* and *Bunyaviridae

The negative-strand RNA virus IAV, member of *Orthomyxoviridae* family, suppresses PB assembly via interaction of NS1 and RAP55; and prevents the sequestering of NP in the PBs (Mok et al., 2012). In contrast, the *Bunyaviridae* hantavirus nucleocapsid protein (N) avoids the 5' cap degradation of cellular mRNAs, protecting them from Dcp1a/Dcp2-mediated decapping which allows the viral transcripts to escape from PBs (Mir et al., 2008) (reviewed in Poblete-Durán et al., 2016).

Paramyxoviridae* and *Rhabdoviridae

Recently, it was shown that the infection of RSV, member of *Paramyxoviridae* family, decreases the number of Dcp1-containing puncta late in infection, suggesting that RSV disassemble PBs over time or that Dcp1 is excluded from PBs (Dickey et al., 2015); while that during early stages of VSV infection, virus belong to *Rhabdoviridae* family, Dcp1/PBs accumulation is unaltered, but further work is necessary to determine its effect on later times (Dinh et al., 2012).

Single Strand RNA Retroviruses (ssRNA-RTs)

Retroviridae

Abrahamyan et al. reported that HIV-1 expression dramatically decreases the number of PBs (Abrahamyan et al., 2010), but the relationship between HIV-1 and the PB components is still controversial. It has been shown that HIV-1 gRNA localize to PBs (Chable-Bessia et al., 2009; Nathans et al., 2009; Martin et al.,

2011), however, that observation has not been reproduced by others (Abrahamyan et al., 2010; Phalora et al., 2012). Similarly, some groups have reported that DDX6, LSM1, GW182, Xrn1, DGCR8, Dicer, and Drosha are antiviral factors, while other researchers argue that Ago2 and DDX6 are proviral factors (Chable-Bessia et al., 2009; Nathans et al., 2009; Martin et al., 2011; Bouttier et al., 2012; Reed et al., 2012). APOBEC3 has been shown to have an anti-HIV-1 activity, but it is targeted for degradation by the viral protein Vif (Poblete-Durán et al., 2016). Interestingly, Chen et al. showed that MOV10 protects A3G from Vif-mediated degradation by interfering with the interaction between Vif and the ubiquitin CBF- β -Cullin 5-ElonginB-ElonginC complex (Chen et al., 2017). In addition, MOV10 increases the incorporation of A3G in HIV-1 viral particles, enhancing the antiviral effect of A3G (Chen et al., 2017). Recently, it has been shown HIV-1 infected monocyte-derived macrophages (MDMs) show diminished levels of Upf1, Upf2, and SMG6 proteins, accordingly with their restrictive role in HIV-1 replication due to their ability to inhibit genomic RNA expression (Rao et al., 2019a). Interestingly, Reed et al. demonstrated that the first assembly intermediate (AI) in which Gag interacts with genomic RNA—containing HIV-1 Gag, GagPol, and Vif (Lingappa et al., 1997)—are formed by the recruitment of DDX6 and ATP-binding cassette protein E1 (ABCE1), suggesting that HIV-1 hijack PB-components to promote viral assembly (Reed et al., 2012; Barajas et al., 2018). The Feline Immunodeficiency Virus (FIV) also co-opts a cellular RNA granule containing DDX6, ABCE1, and Dcp2 to assembly immature capsids, suggesting that this is a mechanism conserved between primate and non-primate lentiviruses (Reed et al., 2018). It has been reported that HTLV-1 Tax protein interferes with host NMD by its interaction with Upf1 and INT6 (Mocquet et al., 2012). In addition, Tax increases the localization of Upf1 in PBs, causing an increase in their size and number. Interestingly, viral RNA is sensitive to degradation via NMD and it has been shown that a fraction of viral genomic RNA co-localized with PBs (Mocquet et al., 2012; Nakano et al., 2013). Fiorini et al. reported that Tax stabilizes the SMG5 and Upf1 interaction, which inhibits Upf1 recycling for another round of NMD (Mocquet et al., 2012). Moreover, Tax inhibits Upf1 binding to its substrate and also destabilizes Upf1 during both unwinding and translocation, promoting its dissociation from the substrate. Together, these observations suggest that Upf1 is targeted by Tax both before and during Upf1-mediated decay (Fiorini et al., 2018). In contrast, Nakano et al. argued that Rex protein is the main protein responsible for NMD inhibition in HTLV-1 infected cells and that Tax effect on NMD is not as significant as the effect of Rex protein (Nakano et al., 2013).

A summary of how viruses modulate PBs can be found in Table 3.

CONCLUDING REMARKS

The knowledge about MLOs has increased exponentially during the last few years (reviewed in Guzikowski et al., 2019).

TABLE 3 | Virus families that modulate PBs.

Genome	Virus family	Virus	PB induction	PB blockade	Mechanism	References
dsDNA	<i>Adenoviridae</i>	Adenovirus	No	Yes	Relocalization of DDX6, LSm1, Ge-1, Ago2, and Xrn1 to aggresomes dependent on E4 11K viral protein Relocalization of Pat1b to aggresomes dependent on E4 11K viral protein	Greer et al., 2011 Friedman and Karen, 2017
	<i>Herpesviridae</i>	Cytomegalovirus (HCMV)	Yes	No	Increased Dcp1a, Edc4, DDX6, and Rap55 protein levels and PB accumulation, but viral mRNA is not sequestered	Seto et al., 2014
Kaposi's sarcoma-associated herpesvirus (KSHV)		No	Yes	PB disruption during lytic replication requires RhoA activation, mediated by vGPCR activation pathway (vGPCR-MK2) PBs disruption during latency requires RhoA activation, mediated by Kaposin B activation pathway (KapB-MK2-hsp27-p11RhoGEF)	Corcoran et al., 2012 Corcoran et al., 2015	
dsRNA	<i>Reoviridae</i>	Rotavirus	No	Yes	Xrn1, Dcp1, and Pan3, but not GW182 protein levels are reduced. NSP1 triggers Pan3 decay. Xnr1 and Dcp1 are translocated to the nucleus PABP is relocalized to the nucleus dependent on the viral protein NSP3 Most of PBs-associated proteins, except DDX6, Edc4, and Pan3, are recruited into RFs	Bhowmick et al., 2015 Montero et al., 2008 Dhillon and Rao, 2018; Dhillon et al., 2018
(+)ssRNA	<i>Flaviviridae</i>	West Nile virus (WNV)	No	Yes	LSm1, GW182, DDX6, DDX3, and Xrn1 are sequestered to RFs	Emara and Brinton, 2007; Chahar et al., 2013
		Dengue Virus (DENV)	No	Yes	LSm1, GW182, DDX6, DDX3, MOV10, and Xrn1 are sequestered to RFs IRAV and MOV10 localizes to RFs and associates with DENV NS4A and NS3 LSm1 binds to the Dengue virus RNA 3' UTR and localizes to viral RFs	Emara and Brinton, 2007; Chahar et al., 2013 Balinsky et al., 2017 Dong et al., 2015
	Zika Virus	No	No	DDX6 and DGCR8 are upregulated in ZIKV-infected neurospheres ZIKV does not affect PBs abundance, morphology or localization ZIKV capsid protein specifically targets nuclear Upf1 for degradation via the proteasome	Garcez et al., 2017 Hou et al., 2017 Fontaine et al., 2018	
	Yellow fever virus (YFV)	Yes*	No	sfRNA co-localizes at PBs and inhibits Xrn1 activity	Silva et al., 2010	
	Kunjin virus (KUNV), Australian strain of DENV	Yes*	No	sfRNA co-localizes at PBs and inhibits Xrn1 activity	Pijlman et al., 2008; Moon et al., 2012	
	Hepatitis C virus (HCV)	Yes*	Yes	DDX6, LSm1, Xrn1, PATL1, Ago2, Dicer, and DDX3 localize to lipid droplets Dcp1 and GW182 not localize to viral factories DDX6 did not colocalize at lipid droplets in hepatocytes from HCV-infected patients XRN1 stalls during exonucleolytic decay of the 5' UTRs of HCV	Ariumi et al., 2011; Berezhna et al., 2011; Pager et al., 2013 Pérez-Vilaró et al., 2012 Pérez-Vilar et al., 2015 Moon et al., 2015	
	<i>Picornaviridae</i>	Bovine Viral Diarrhea Virus (BVDV)	ND	ND	XRN1 stalls during exonucleolytic decay of the 5' UTRs of BVDV	Moon et al., 2015
		Poliovirus (PV)	No	Yes	3C protease-mediated cleavage of Xrn1, Dcp1a, and Pan3 Protease 2A inhibits PB assembly	Dougherty et al., 2011 Dougherty et al., 2015
		Coxsackievirus B3 (CVB3)	No	Yes	3C protease-mediated cleavage of Xrn1, Dcp1a, and Pan3 Cytoplasmic redistribution and cleavage of AUF1, mediated by 2A and 3C protease, respectively	Dougherty et al., 2011 Wong et al., 2013

(Continued)

TABLE 3 | Continued

Genome	Virus family	Virus	PB induction	PB blockade	Mechanism	References
		Encephalomyocarditis virus (EMCV)	ND	ND	Cleavage of MOV10 by 3C protease	Rao et al., 2019b
		Enterovirus 71 (EV-71)	Yes	Yes	Cleavage of MOV10 by 3C protease	Cuevas et al., 2016
					Disrupts DDX6 and Dcp1a foci	Zhu et al., 2016; Yang et al., 2018b
					EV71 2C protein reduces the expression of A3G through autophagy-lysosome pathway	Li et al., 2018
					MOV10 promotes viral RNA replication and IRES-dependent translation	Wang et al., 2016
					MOV10 co-localizes with PBs upon EV71 infection	Wang et al., 2016
	<i>Dicistroviridae</i>	Cricket paralysis virus (CrPV)	Yes	Yes	Disrupts aggregates containing GW182 and Dcp1	Khong and Jan, 2011
	<i>Togaviridae</i>	Sindbis virus (SINV)	No	Yes	Viral RNA interacts with HuR	Sokoloski et al., 2010
					Upf1 is a restriction factor for SINV	Balistreri et al., 2014
		Semliki Forest Virus (SFV)	ND	ND	Upf1 is a restriction factor for SFV	Balistreri et al., 2014
	<i>Coronaviridae</i>	Mouse Hepatitis Coronavirus (MHC)	Yes	No	Induces host translational shutoff	Raaben et al., 2007
		Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	ND	ND	SCoV nsp1-mediated promotion of host mRNA degradation	Kamitani et al., 2009; Huang et al., 2011
		Transmissible Gastroenteritis Virus (TGEV)	No	Yes	Decreases the number of PBs	Sola et al., 2011
(-)ssRNA	<i>Orthomyxoviridae</i>	Influenza virus A (IAV)	No	Yes	NS1 interacts with RAP55, Ago1, Ago2, and Dcp1a	Mok et al., 2012
	<i>Bunyaviridae</i>	Hanta virus	Yes*	No	Cap snatching occurs in PBs	Mir et al., 2008
	<i>Paramyxoviridae</i>	Respiratory Syncytial Virus (RSV)	ND	ND	Reduction of Dcp1 puncta over time	Dickey et al., 2015
	<i>Rabdhoviridae</i>	Vesicular stomatitis virus (VSV)	ND	ND	Dcp1 puncta are not affected	Dinh et al., 2012
ssRNA-RT	<i>Retroviridae</i>	Human Immunodeficiency virus type 1 HIV-1	ND	Yes	HIV-1 genomic RNA interacts with DDX6, Ago2, and APOBEC3G	Nathans et al., 2009
					Relocalization of PBs out of zones where genomic RNA accumulates	Abrahamyan et al., 2010
					The first assembly intermediate where Gag interacts with viral RNA contains DDX6 and ABCE1	Reed et al., 2012; Barajas et al., 2018
					Overexpression of MOV10 inhibits HIV-1 replication	Burdick et al., 2010
					MOV10 inhibits the degradation of APOBEC3G through interference with the Vif-mediated ubiquitin-proteasome pathway	Dong et al., 2015
					Downregulation of Upf1, Upf2, and SMG6 in infected monocyte-derived macrophages	Rao et al., 2019a
		Feline Immunodeficiency Virus (FIV)	ND	ND	Assembly intermediates are formed by DDX6, Dcp2, and ABCE1	Reed et al., 2018
		Human T-cell lymphotropic virus type I (HTLV-1)	Yes	No	Tax inhibits NMD by targeting Upf1 and INT6	Mocquet et al., 2012; Fiorini et al., 2018
					Tax increases the localization of Upf1 in PBs	Mocquet et al., 2012
					A fraction of viral RNA colocalizes in PBs	Mocquet et al., 2012; Nakano et al., 2013
					Rex inhibits Upf1 activity	Nakano et al., 2013

*Maintain PB endogenous.

Consequently, the historically proposed roles of SGs and PBs in mRNA storage and degradation have been challenged. SGs and PBs assembly have been shown to contribute to cell survival, inducing translational arrest and delay apoptosis by sequestration of RACK1 from JNK, while that SGs may inhibit growth signaling by diverting TORC1 from its active location at lysosomes (Arimoto et al., 2008; Kedersha et al., 2011; Thedieck et al.,

2013; Arimoto-Matsuzaki et al., 2016). Single-molecule imaging studies have revealed that mRNAs can transiently interact or move between SGs and PBs (Wilbertz et al., 2018; Moon et al., 2019), and more interestingly, that mRNA translation and degradation dynamics are equivalent for MLO-engaged and “free” mRNAs, suggesting that their sequestration into granules does not regulate translation and decay (Wilbertz et al., 2018).

Recently, Niewidok et al. revealed the existence of a relative immobile nanocore within SGs and a mobile outer liquid phase that allows a dynamic exchange of protein and mRNA between SGs (Niewidok et al., 2018). Importantly, the tight interaction between SG-nanocores and prion-like domains present in many SG and PB components has been proposed as a potential origin of neurotoxic protein aggregates that are linked to the progression of different neurodegenerative diseases (reviewed in Ramaswami et al., 2013; Dobra et al., 2018), growing MLOs as an attractive therapeutic target for the treatment of such syndromes. A similar interest is rising regarding MLOs and viral infections. As reviewed here, cellular and viral-induced MLOs have been associated with a spatiotemporal regulation of viral replication, viral assembly and host immune evasion (Schuster et al., 2018). MLOs allow the concentration of viral proteins and viral genome in the cytosol of infected cells, enabling a dynamic exchange and adaptation to changing environmental conditions. Despite all the information presented in this review about the modulation of the MLOs assembly, many molecular details of how some viral families proceed to subvert the MLOs remain unknown. Why some viruses promote or inhibit the MLO assembly is well-characterized. In many cases, these MLOs serve as viral factories recruiting cellular proteins to ensure efficient viral replication, while that the co-option of proteins involved in antiviral response (e.g., interferon-stimulated genes) could have a detrimental effect. On the other hand, the dynamism in the MLOs assembly/disassembly over the course of a viral infection would allow the chronicity of the infection (Ruggieri et al., 2012). Today, we know that not only proteins, but also RNA modifications

have gained importance in the fate of mRNAs inside the cell. These RNA modifications (e.g., m6A, m5C) have been involved in triaging mRNAs to RNA granules (Anders et al., 2018) which have also been widely identified in the RNA genomes of several viruses such as HIV-1, ZIKV, HCV, IAV, KSHV, and SV40 (Reviewed in Pereira-Montecinos et al., 2017; Manners et al., 2018). Thus, the possibility to develop drugs that upregulate these pathways, the generation of molecules that disaggregate or target crucial viral-MLO interactions arises to impair viral replication (Jackrel et al., 2014). Furthermore, due to the shared mechanism that different viruses use to modulate MLOs, drugs targeting MLOs could eventually serve as broad-spectrum antivirals for infectious diseases.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This review was supported by Conicyt Chile through the Fondecyt No. 1180798 (FV-E) and Conicyt grant No. 21181508 (AG-A).

ACKNOWLEDGMENTS

We thank Andrew Mouland for providing comments on this manuscript.

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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.

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