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Review

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Antiviral innate immunity and stress granule responses

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Viral infection triggers the activation of antiviral innate immune responses in mammalian cells. Viral RNA in the cytoplasm activates signaling pathways that result in the production of interferons (IFNs) and IFN-stimulated genes. Some viral infections have been shown to induce cytoplasmic granular aggregates similar to the dynamic ribonucleoprotein aggregates termed stress granules (SGs), suggesting that these viruses may utilize this stress response for their own benefit. By contrast, some viruses actively inhibit SG formation, suggesting an antiviral function for these structures. We review here the relationship between different viral infections and SG formation. We examine the evidence for antiviral functions for SGs and highlight important areas of inquiry towards understanding cellular stress responses to viral infection.

Viral infection and stress granules

Viral invasion and replication are detected by innate immune sensors in cells, triggering downstream signaling pathways that can ultimately result in the activation of systemic immune responses. Several innate immune sensors recognize cytoplasmic viral RNA [1], and lead to the production of IFNs which in turn trigger various antiviral pathways aimed at halting viral replication and spread. These antiviral effects include double-stranded (ds) RNA-dependent protein kinase (PKR)-dependent inhibition of mRNA translation, and 2′,5′-oligoadenylate synthetase (OAS)/RNase L-mediated RNA degradation [2]. Innate immune responses also trigger the activation of adaptive immunity in the form of T and B cell activation and proliferation, and modulate the phenotype and function of these adaptive responses [3,4].

In some cases, viral infection also induces the formation of cytoplasmic granules similar to those induced by cellular stresses such as heat, oxidation, hypoxia, and osmotic pressure, which are referred to as stress granules (SGs). SGs are ribonucleoprotein (RNP) aggregates that contain translationally stalled mRNAs, 40S ribosomes, and various RNA-binding proteins [5–7] (Box 1).

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Activation of the RLR signaling pathways by viral RNA

Innate immune responses are triggered upon recognition of pathogen-associated molecular patterns (PAMPs) which in the case of viruses are often nucleic acid-based, either RNA or DNA. Viral nucleic acid can be detected by sensors including Toll-like receptors (TLR)3, 7/8, and 9, retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), and cytoplasmic DNA sensors such as DNA-dependent activator of IFN-regulator factors (DAI), stimulator of IFN genes (STING, also known as MITA/ERIS/MPYS), DEAD box polypeptide 41 (DDX41), and cGMP/cAMP synthase (cGAS) [8–12]. RLRs, RIG-I, melanoma differentiation-associated protein 5 (MDA5), and DHX58 [DEXH (Asp-Glu-X-His) box polypeptide 58, also known as LGP2] are all RNA helicases and contain the signature DExD/H motif that characterized the DExD/H box family. These proteins are crucial for the detection of cytoplasmic RNA [13,14]. RLRs discriminate self from viral transcripts by recognizing specific biochemical signatures such as ds structure and the presence of a 5′-ppp moiety [15–17]; self-transcipts lack these viral signatures.

The signaling pathways downstream of the founding member of the RLR family, RIG-I, are among the best understood. Upon viral RNA recognition by RIG-I, the signal is relayed to the adaptor protein IFN-β promoter stimulator 1 (IPS-1, also known as MAVS, VISA, or Cardif), which predominantly localizes to the mitochondrial outer membrane [18,19]. When viral RNA binds at the helicase and the C-terminal domain (CTD) of RIG-I, its N-terminal caspase recruitment domains (CARDs) are covalently modified with K63-linked polyubiquitin chains by the E3 ligase, tripartite motif-containing protein 25 (TRIM25) [20], and oligomerize [21]. The ubiquitinated and oligomerized CARDs bind to the CARD domain on IPS-1 on mitochondria, peroxisomes, and/or mitochondrion-associated membrane (MAM) regions in the endoplasmic reticulum (ER) [22]. The translocation of RIG-I to these locales is facilitated by the chaperone protein 14-3-3ε [23]. The requirement for K63-linked polyubiquitin chains is complex because several reports have demonstrated the importance of non-covalent interaction between RIG-I CARDs and the unanchored K63–ubiquitin chains [21,24].

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Box 1. An overview of SG biology

Cells respond to various insults including heat, oxidative stress, nutrient starvation, and proteotoxic stress by forming cytoplasmic nucleoprotein aggregates termed SGs [5,68–70]. Multiple RNA-binding proteins (RBPs) localize to SGs, and some have been used as markers for these cytoplasmic bodies (Table I). Although the formation of SGs in live cells can be detected by monitoring fluorescence-tagged SG marker proteins, biochemical isolation of SGs is notoriously challenging because these are not membrane-sequestered compartments.

SG formation has been interpreted as a response aimed at preventing the generation of abnormal proteins by transient stalling of translation in times of cellular stress. Stalled transcripts undergo translation upon recovery from stress, or alternatively they are degraded in another granular compartment termed the processing body (P-body, PB) [71,72]. Unlike SGs, PBs are present in the unstressed cell, and contain enzymes for mRNA degradation such as decapping enzymes and 5′–3′ exonucleases (Table I). It is thought that transcripts and proteins can move from SGs to PBs (and vice versa), and these aggregates share some of their components (Table I) [60]; however, the mechanisms underlying the proposed exchange of contents are unclear.

SG proteins, as defined by studies using proteins characteristic to SGs as markers [73], are either diffusely distributed in the cytoplasm or localized in the nucleus in normal conditions; stress triggers their aggregation in the cytoplasm [5,74]. A common event downstream from the aforementioned cellular stresses is phosphorylation of eIF2α at serine 51, which is considered to be an initial trigger for SG formation. Four eIF2α kinases, PKR, GCN2, PKR-like endoplasmic reticulum kinase (PERK), and heme-regulated eIF2α kinase (HRI), can phosphorylate eIF2α in mammals (Table II). The mechanisms that connect eIF2α phosphorylation to SG formation remain to be elucidated.

Some proteins have been shown to be crucial for the formation and or stability of SGs. These include G3BP1, a phosphorylation-dependent endonuclease [30,75], and T cell restricted intracellular antigen-1 (TIA1) and TIA-related protein (TIAR) that are collectively termed TIA1/TIAR [74,76]. Removal of these regulators by genomic deletion or RNAi blocks SG formation by sodium arsenite, and a mutant form of G3BP1 (S149E) acted as a dominant inhibitor of SG formation [75]. However, because of analytical constraints, the molecular machinery underlying the formation of SGs remains unclear.

Table I. Protein components of SGs and P-bodies.

Factor	Full name	Functions	Refs
SG components			
ADAR	Adenosine deaminase, RNA-specific	RNA editing, RNA stability	[77]
Caprin-1	Cell cycle associated protein 1	Cell growth, SG assembly	[44,78]
phospho-eIF2α	Eukaryotic translation initiation factor 2A	Initiation factor, SG assembly	[60,79]
eIF3	Eukaryotic translation initiation factor 3	Multisubunit initiation factor	[5]
eIF4G	Eukaryotic translation initiation factor 4G	Initiation factor	[5]
G3BP1	Ras-GTPase-activating protein SH3-domain-binding protein 1	Endoribonuclease, ras signaling, SG assembly	[75]
HDAC6	Histone deacetylase 6	Translation regulator, SG assembly	[80]
HuR/ELAVL1	Hu antigen R/ELAV-like RNA-binding protein 1	mRNA stability, translation regulator	[5,81]
OGFOD1	2-Oxoglutarate and iron-dependent oxygenase domain containing 1	Translation regulator, SG assembly	[82]
PABP1	PolyA-binding protein 1	mRNA stability, translation regulator	[74]
Pum1	Pumilio RNA-binding family member 1	Translation regulator, cell growth	[83]
Pum2	Pumilio RNA-binding family member 2	Translation regulator, SG assembly	[84]
RHAU/DHX36	RNA helicase associated with AU-rich element/DEAH box polypeptide 36	RNA helicase, SG assembly, antiviral activity	[49,85]
SMN	Survival of motor neuron	RNA metabolism, SG assembly	[86,87]
STAU1	Staufen dsRNA-binding protein 1	RNA transport, SG assembly	[88]
TIA1	T cell restricted intracellular antigen-1	Translation regulator, SG assembly	[74,76]
TIAR	TIA-1-related protein	Translation regulator	[74]
ZBP1	Z-DNA-binding protein 1	DNA sensor, translational regulator	[11,89]
40S	Eukaryotic small ribosomal subunit	Ribosome	[5]
P-body components			
CNOT6/CCR4	CCR4–NOT transcription complex, subunit 6	mRNA deadenylation, PB assembly	[90,91]
DCP1a	Decapping mRNA 1A	mRNA decapping	[60,92]
DCP2a	Decapping mRNA 2A	mRNA decapping	[60,92]
EDC4/GE-1/Hedls	Enhancer of mRNA decapping 4	Decapping coactivator, PB assembly	[93,94]
TNRC6A/GW182	Trinucleotide repeat-containing 6A/GW bodies 182	RNA silencing, PB assembly	[95,96]
Lsm1	Lsm1, U6 small nuclear RNA associated	Decapping coactivator, PB assembly	[90,92,97]
SG and PB components			
APOBEC3G	Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G	Antiviral activity	[98,99]
Ago2	Argonaute RISC catalytic component 2	RNA silencing, PB assembly	[100,101]
BRF1	Butyrate response factor 1	ARE-mediated mRNA decay	[60]
CPEB	Cytoplasmic polyadenylation element binding protein	Polyadenylation, translation regulator	[102]
DDX3	DEAD box helicase 3	RNA helicase, antiviral activity	[103,104]

Table I (*Continued*)

SG and PB components			
DDX6/RCK	DEAD box helicase 6	RNA helicase, antiviral activity, PB assembly	[90,102,105]
FAST	Fas-activated Ser/Thr kinase	Splicing regulator	[60]
RAP55/LSM14A	RNA-associated protein 55	PB assembly, antiviral activity	[11,106]
TTP	Tristetraprolin	ARE-mediated mRNA decay	[60]
Xrn1	5′-3′ Exoribonuclease 1	5′–3′ exonuclease	[60,92]

Table II. Kinases that target eIF2α.

Kinase	Full name	Stress	Refs
PKR	dsRNA-dependent protein kinase	dsRNA, viral RNA, viral infection	[107,108]
PERK	PKR-like ER kinase	ER stress, hypoxia	[109–111]
GCN2	General control non-derepressible 2	Nutrient deprivation, amino acid deprivation, viral infection	[28,112]
HRI	Heme-regulated eIF2α kinase	Heat shock, oxidative stress, osmotic stress	[113,114]

Furthermore, it has been reported that RIG-I forms a signaling-competent filament on substrate dsRNA independently of ubiquitins [25]. Although a recent structural report suggests that the conformation of the active tetramer of RIG-I CARDs can be stabilized by covalent conjugation with ubiquitin chains, and that filament formation may partially compensate for ubiquitin-dependent RIG-I activation [26], further analysis will be necessary to clarify the molecular role of ubiquitin chains in RIG-I signaling. The RIG-I/IPS-1 interaction recruits signaling molecules including tumor necrosis factor (TNF) receptor-associated factors (TRAFs). Subsequent activation of TANK-binding kinase 1(TBK1)/inducible IκB kinase (IKKi), and IKKα/IKKβ induces downstream signaling via the IFN regulatory factor (IRF) and nuclear factor-κB (NF-κB) pathways, respectively. These pathways ultimately culminate in the activation of the transcription factors IRF-3, IRF-7, and NF-κB, which activate the transcription of IFN and proinflammatory cytokine genes [27]. These pathways are summarized in Figure 1. Moreover, secreted IFN amplifies the expression of ISGs, such as RLRs, PKR, and OAS, as a host strategy to amplify antiviral signaling.

Induction of SGs by viral infection

Viruses, particularly RNA viruses, have been shown to induce the formation of SG-like cytoplasmic bodies (Table 1

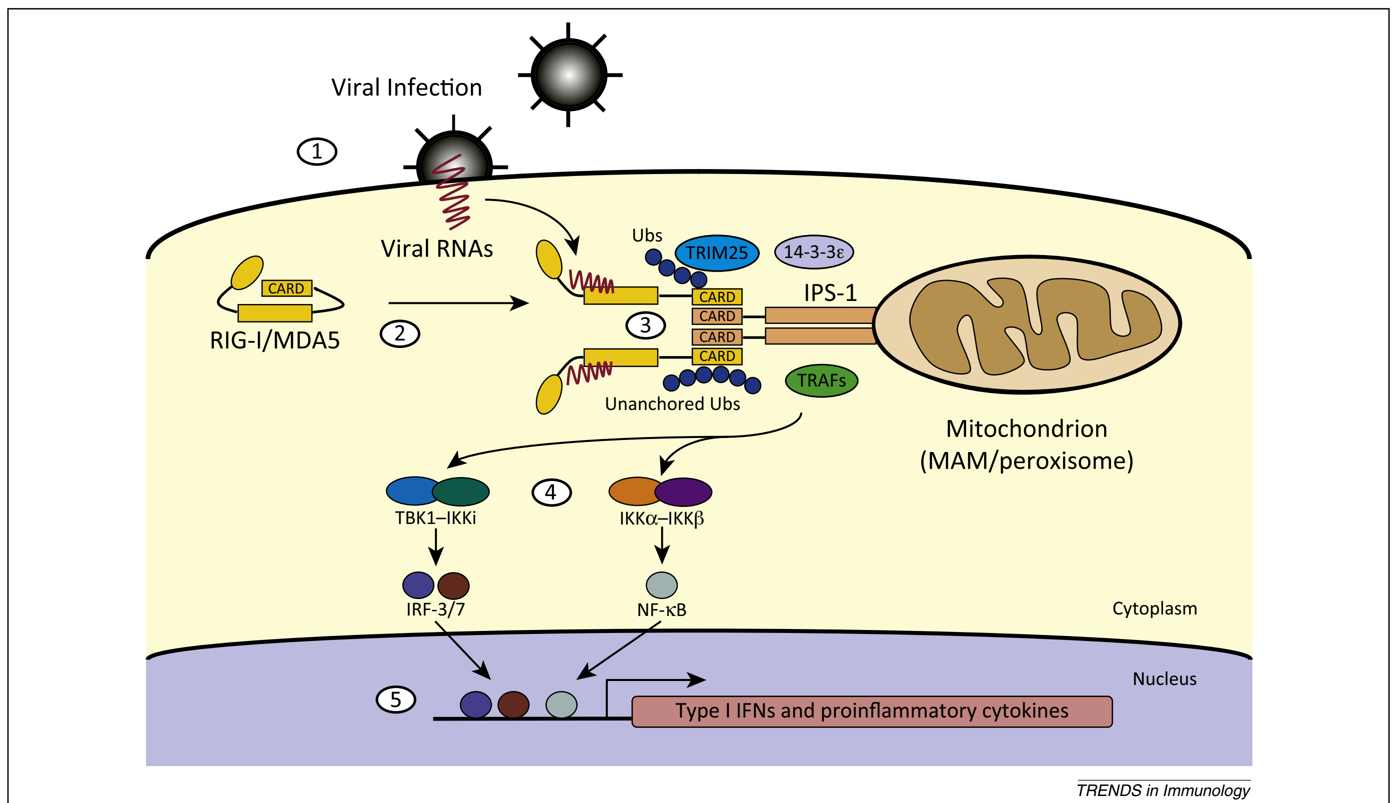

Figure 1. Detection of viral RNA by RLR [retinoic acid inducible gene I (RIG-I)-like receptor]. (1) Viral internalization and release of the RNA genome in the cytoplasm. (2) Autorepressed RIG-I or MDA5 bind to viral RNA and undergo a conformational change to expose CARD and associate with IPS-1 via CARD–CARD interactions. (3) Signaling proteins are recruited around the RLR/IPS-1 complex and (4) activate the TBK1/IKKi–IRF-3/7 and IKKα/IKKβ–NF-κB pathways, resulting in (5) the activation of type I IFNs and proinflammatory cytokines.

Table 1. Viral infection and SG formation.

Family	Species	Genome	SG formation	Mechanism of inhibition or activation	Refs
Picornaviridae	Poliovirus	ssRNA (+ sense)	Yes (transient)	G3BP1 cleavage by 3C protease	[30,67]
	EMCV	ssRNA (+ sense)	Yes (transient)	G3BP1 cleavage by 3C protease	[29]
	Mengovirus	ssRNA (+ sense)	No	Inhibition by leader protein	[37]
	TMEV	ssRNA (+ sense)	No	Inhibition by leader protein	[37]
Togaviridae	Sindbis virus	ssRNA (+ sense)	Yes (transient)	PKR-and GCN2-dependent. tRNA-like motifs in the genome are responsible for GCN2 activation	[28,29]
	SFV	ssRNA (+ sense)	Yes (transient)		[33]
	Rubella virus	ssRNA (+ sense)	No		[115]
Flaviviridae	West Nile virus	ssRNA (+ sense)	No	Recruitment of TIA/TIAR to replication complexes	[48,116]
	Dengue virus	ssRNA (+ sense)	No	Recruitment of TIA/TIAR to replication complexes	[48]
	JEV	ssRNA (+ sense)	No	Core protein interacts with caprin 1	[44]
	HCV	ssRNA (+ sense)	Yes	5′-UTR of HCV genome activates PKR	[34–36, 117,118]
Nidoviridae	Coronavirus	ssRNA (+ sense)	Yes	Host polypyrimidine tract-binding protein is essential	[119]
	Mouse hepatitis virus	ssRNA (+ sense)	Yes		[120]
Rhabdoviridae	VSV	ssRNA (– sense)	Yes or no? (strain-dependent?)		[29,121]
Paramyxoviridae	Sendai virus	ssRNA (– sense)	No	Inhibition of PKR activation by C and V proteins Viral trailer RNA also inhibits SG through interacting with TIAR	[45,46]
	Measles virus	ssRNA (– sense)	No	C protein activates ADAR, resulting in PKR inhibition	[39]
	RSV	ssRNA (– sense)	Yes	PKR-dependent. Trailer RNA inhibits SG formation	[122–124]
Orthomyxoviridae	Influenza virus	ssRNA (– sense, segmented)	No	NS1 blocks PKR activation	[41–43]
Arenaviridae	Junin virus	ss Ambisense RNA	No	Nucleoprotein and glycoprotein precursor are implicated to inhibit eIF2α phosphorylation	[125]
Reoviridae	Reovirus	dsRNA (segmented)	Yes (Transient)	Involvement of ATF accumulation in SG disassembly is suggested	[32,126,127]
	Rotavirus	dsRNA (segmented)	No	Inhibition by NSP3?	[47]
Adenoviridae	Adenovirus	Linear dsDNA	No	Inhibition by E1A	[29]
Poxviridae	Vaccinia virus	dsDNA	No	Inhibition by E3L	[128,129]
?	Cricket paralysis virus	ssRNA (+ sense)	No	Viral infection inhibits SG by unknown mechanisms	[130]

and references therein). In some cases these bodies have been given different names in an attempt to distinguish them from SGs; in this review, however, we refer to virus-induced SG-like granules collectively as SGs. Many viruses induce SGs through the activation of the eukaryotic translation initiation factor (eIF)2α kinases PKR and, in some cases, general control non-depressible 2 (GCN2), which are both triggered by detection of RNA in the cytoplasm [28] (Figure 2). Depending on both the virus and the host cell, different patterns of SG formation have been observed upon infection: stable SG formation, no SG formation, transient SG formation, or alternating (oscillating) SG formation in which SGs form, disperse, and reform during the assays (Table 1).

Transient SG formation results from dissociation of key components in SGs by viral proteins [29–33]. For instance, in the case of infection of several picornaviruses, such as poliovirus, coxsackievirus and encephalomyocarditis virus (EMCV), transient formation of SGs is associated with the cleavage of Ras-GAP SH3 domain binding protein-1 (G3BP1) by the viral 3C protease [29–31]. This was confirmed by the observation that ectopic expression of cleavage-resistant G3BP1 leads to stable SG formation. On the other hand, recent studies have demonstrated that infection with hepatitis C virus (HCV) produces oscillating SGs [34]. HCV strongly activates PKR via the 5′-untranslated region (UTR) of its genome [35], thereby inducing SGs [34,36], but stress-inducible expression of growth arrest DNA-damage-inducible 34 (GADD34), a regulatory component of host protein phosphatase 1 (PP1), leads to dephosphorylation of eIF2α and terminates SG formation. In the stress-recovered condition, GADD34 protein is rapidly downregulated by an unknown mechanism and the phosphorylated form of eIF2α reaccumulates in the cells, resulting in an oscillating pattern of SGs.

Inhibition of SG formation by viruses: an antiviral role for SGs?

In cases where viral infection appears to not induce SGs, accumulating evidence suggest that these viruses inhibit

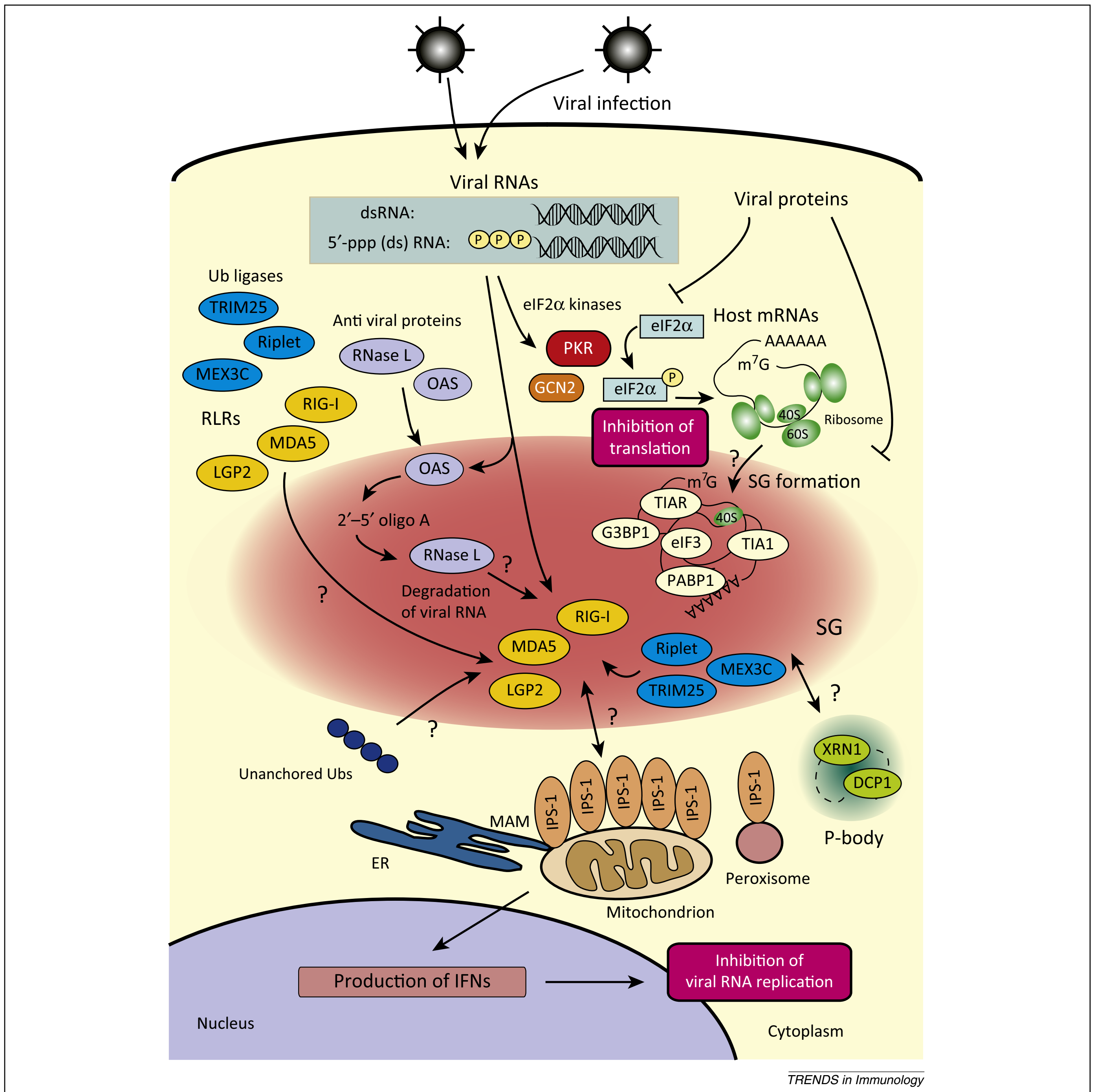

Figure 2. A model for antiviral function of stress granules (SG). In virus-infected cells, viral RNAs activate PKR (or GCN2, in the case of Sindbis virus) to initiate assembly of SG through eIF2α phosphorylation. eIF2α phosphorylation blocks translation of cellular mRNAs. Translation-stalled mRNAs may be transferred to a distinct cellular compartment, the P-body, to be degraded. Viral RNAs are also recognized by RLRs, which are recruited to SGs with several signaling molecules including antiviral proteins and ubiquitin ligases. The OAS–RNase L pathway cleaves viral RNAs, and the cleaved RNAs may act as ligands for RLRs. IPS-1, which is localized on mitochondria and/or MAM, forms prion-like aggregates, interacts with RLRs on SGs, and activates IFN-inducing signaling. Areas that require further investigation are highlighted with question marks.

SG formation. Cells infected with mengovirus or Theiler's murine encephalomyelitis virus (TMEV), which belong to the *Cardiovirus* genus within the family of *Picornaviridae*, do not exhibit SGs, and this has been proposed to be due to complete inhibition of SG formation by the viral nonstructural protein, leader (L) protein [37]. Although L protein is known to block IFN production via inhibition of IRF-3 activation [38], it remains unknown how L limits SG formation.

Similarly, SGs do not form upon infection of cells with measles virus. In this case the mechanism proposed involves the viral C protein because C-deficient virus, but not the wild type, strikingly induces SGs [39]. Although measles C protein has diverse functions during infection, including modulation of viral polymerase activity and inhibition of IFN production [40], the molecular machinery for SG inhibition remains to be determined.

In the case of influenza A virus (IAV), the viral nonstructural protein 1(NS1) has been shown to inhibit eIF2α phosphorylation by blocking PKR activation via viral RNA sequestration and physical interaction [41–43]. During IAV infection, the viral nucleocapsid initially accumulates in the nucleus and is then transported to the cytoplasm in the late phase of infection. However, in a mutant IAV lacking NS1, the viral nucleocapsid was reported to coincide with SGs in the cytoplasm, to which RIG-I is colocalized [42]. These findings suggest that SGs function as a platform for the detection of IAV genomic RNA by RIG-I.

As in the cases of mengovirus, TMEV, and measles virus, there appears to be a clear benefit, from the standpoint of the virus, to interfering with SG formation. An implication of these findings is that SGs have an antiviral role and that, accordingly, viruses have developed strategies to suppress their formation (Figure 2). Indeed, there are multiple examples of viruses actively inhibiting the formation of SGs through varied mechanisms [44–48]. An inverse correlation between SG formation and viral propagation has been reported in multiple viral replication systems. In the case of Japanese encephalitis virus (JEV) infection, SG formation is inhibited by the viral core protein, which directly interacts with SG component, caprin 1 [44]. In cells infected with a mutant virus whose core protein fails to interact with caprin 1, inhibition of SG formation is abrogated and viral propagation is significantly impaired both *in vitro* and *in vivo*, suggesting that SGs impact negatively on viral replication. This notion is further supported by studies showing that RLRs localize to virus-induced SGs, suggesting that SGs may act as a platform for viral RNA sensing and the activation of downstream signaling pathways [42]. There is a strong correlation between PKR-dependent SG formation and IFN production in some viral infections [29,42,49] (Figure 2). However, a recent study has demonstrated that PKR-dependent accumulation of MDA5 in SGs is dispensable for triggering IFN responses [50]. Further investigations will be necessary to address this discrepancy.

Whether PKR is required for virus-induced IFN production is controversial. Some reports indicate that IFN production is significantly impaired in PKR-deficient cells [29,42,49,51–55], whereas others show that deficiency of PKR has no effect [54,56–58]. One possible explanation for these observations is that there are differences in the viruses and cell types used in each study. In the early 2000s, several studies demonstrated that virus-induced activation of IFN is independent of PKR in plasmacytoid dendritic cells (pDCs), which are known to be 'IFN-producing cells'. However, subsequent reports revealed that robust IFN induction by pDCs is exclusively induced by TLRs, suggesting a dispensable role for PKR in TLR-mediated signaling. By contrast, the PKR-dependency of RLR-mediated signaling is more complicated. Because viruses are extraordinary diverse in their genome structures and life cycles, different viruses are likely to produce different RNA species during viral replication at distinct locations in the infected cells. Thus, the ability of these viral RNAs to activate PKR and/or RLRs could be divergent. Moreover, as mentioned above, viruses employ a variety of strategies to terminate antiviral responses. For instance, it has been demonstrated that Sendai virus (SeV)-induced IFN production is independent of PKR [53,54]. Indeed, infection of SeV can activate IFN without SG formation [29]; however, infection by a mutant virus in which accessory protein C is deleted leads to significant activation of PKR and eIF2α phosphorylation, with concomitant upregulation of IFN [45,59], suggesting that PKR is dispensable for SeV-induced IFN activation, but is responsible for the enhancement of IFN production. Thus, the PKR-dependency of IFN production might vary depending on the ability of each virus to modulate host responses. This notion is supported by reports in which IFN production following stimulation with a virus-mimetic synthetic dsRNA such as poly(I:C) showed significant PKR-dependency [29,42,49,53,55].

Understanding the relationship between mechanisms of viral detection and SGs

During viral infection, viral RNA, either incoming or produced as a replication intermediate, triggers a series of events. DsRNA activates PKR (or GCN2) to initiate assembly of SG via eIF2α phosphorylation, and this in turn blocks translation and leads to the recruitment of stalled transcripts into SGs (Box 1 and Figure 2). It has been proposed that, if the stress stimulus is not resolved, the stalled transcripts are transferred to processing bodies (P-bodies, PBs) for degradation [60]. This view requires reexamination because SG formation does not necessarily result in translational shut-off. Indeed, it is unclear whether SG formation results in total host cell translational shut-off or translational arrest at limited areas in the cytoplasm. Many viruses hijack host cellular compartments to form replication complexes for viral transcription and translation [61,62]. The fact that IFN is efficiently translated in virus-infected and SG-containing cells [29,42,49] suggests that SG formation does not necessarily correlate with total host translational shut-off.

Viral dsRNA contained in SG potentially activates OAS to catalyze the synthesis of 2′-5′ oligo A, which activates cytoplasmic endoribonuclease RNase L [63]. RNase L is also detected in SGs of virus-infected cells [42]. Activated RNase L may cleave viral RNA in SG to block viral transcription and translation, and some cleavage products may act as ligands for RLR [64]. Several ubiquitin ligases including TRIM25, RING finger protein leading to RIG-I activation (Riplet), and mex-3 RNA binding family member (MEX3C), that are known to regulate RIG-I activation, are also colocalized in virus-induced SG (Figure 2) [65,66]. Although several studies suggest that RLR might be activated in virus-induced SGs [29,42,49], direct evidence to this effect is lacking. RLR-mediated signaling is transmitted via homotypic interaction with IPS-1, which is localized on mitochondria, peroxisomes, and MAMs. It is unclear how RLR-containing SGs can communicate with these organelles and activate antiviral signaling (Figure 2).

A major challenge for SG research is that SGs are difficult entities to isolate for biochemical analyses. The composition of SGs induced by different viruses and in different host cells may vary [49,67]. The development of novel biochemical isolation approaches and molecular probes for cell biological

analyses will be crucial in investigating the molecular events taking place in SGs during viral infection.

Concluding remarks and future directions

Stress responses are known to be crucial for maintaining the homeostasis of living organisms. In response to various stresses, eukaryotic cells initiate stress responses, including the formation of SGs, in which cytoplasmic mRNAs are compartmentalized to escape dysregulation. Accumulated lines of evidence show that viral infection can also induce stress responses including SG formation concurrently with the initiation of innate antiviral responses via pattern recognition receptors (PRRs). The observations that (i) there is a strong correlation between SG formation and IFN production, (ii) there is a reverse correlation between SG formation and viral propagation, and (iii) RLRs are localized in viral-induced SGs together with viral non-self RNAs, together strongly suggest that SGs have an antiviral role and possibly function as platform to initiate innate responses. Interestingly, this notion clearly indicates that the quality control machinery for 'self RNA' and the host defense mechanism against invasion of 'non-self RNA' are closely coordinated with each other. Moreover, it is interesting to note that these observations may help us to develop a novel therapeutic or preventive strategy for virus-induced infectious diseases.

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