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To cite this article: Rachel Kim , Erika N. Calle Urgiles & Stephanie L. Moon (2026) Stress granules at the crossroads of the proteostasis network, RNA Biology, 23:1, 1-22, DOI: [10.1080/15476286.2026.2731904](https://doi.org/10.1080/15476286.2026.2731904)

To link to this article: <https://doi.org/10.1080/15476286.2026.2731904>



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Published online: 12 Oct 2026.



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Stress granules at the crossroads of the proteostasis network

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ABSTRACT

The proteostasis network maintains cell function by safeguarding the proteome through the coordinated actions of protein synthesis, quality control, and degradation machinery including chaperones and the ubiquitin-proteasome system. Proteostasis collapse and activation of the integrated stress response (ISR) occur in ageing and neurodegeneration. Upon proteotoxic stress, translation suppression during the ISR drives the assembly of non-translating mRNAs into biomolecular condensates called stress granules. Stress granules act as a double-edged sword in the proteostasis network, serving beneficial or detrimental roles through their effects on translation, protein quality control, and protein aggregation. In this review, we discuss how protein synthesis, quality control, and degradation factors regulate stress granule dynamics, and conversely how stress granules impact proteostasis. While stress granules may initially protect cells by sequestering misfolded, aggregation-prone proteins and regulating translation, they may evolve into sites of pathological aggregation. Clarifying these intersections may reveal therapeutic strategies for neurodegeneration and other disease processes.

ARTICLE HISTORY

Revised 2 September 2026
Accepted 4 September 2026

KEYWORDS

Proteostasis; stress granules; translation; protein quality control; integrated stress response

Introduction

Protein homeostasis (proteostasis) is critical for cellular resilience and survival in the face of endogenous and exogenous stressors. Proteostasis is the balance of, and feedback between, protein synthesis, folding, localization, quality control, and degradation, allowing for proper protein function and aggregate prevention [1–4]. The proteostasis network is composed of translation machinery, chaperones, protein trafficking systems, and degradation systems such as the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. It spans multiple cellular compartments including the nucleus, endoplasmic reticulum (ER), mitochondria, and cytosol [5]. The proteostasis machinery ensures protein quality control while eliminating damaged proteins that cannot be repaired [5,6]. This is especially critical during stress, where the chaperone network resolves misfolded proteins including nascent polypeptides that could accumulate from stressors, such as oxidative stress and heat, and lead to aberrant aggregation if not properly regulated [2,6,7]. Loss of proteostasis resulting from impaired protein synthesis or co-translational protein quality control, accumulation of damaged or misfolded proteins, and reduced protein turnover is associated with ageing and ageing-associated neurodegenerative diseases [1,2,8–11]. Therefore, defining mechanisms of proteostasis may suggest therapeutic approaches for these and other disorders.

Stress granules (SGs) are biomolecular condensates in the cytoplasm that form under cellular stress conditions including heat, cold, oxidative or ER stress, inflammation, toxic metalloid exposure, viral infections and others [12–17]. Stress granules assemble through RNA-RNA, RNA-protein, and protein-protein interactions driven by release of mRNA from the translating pool during stress [18–21]. Although the functions of SGs are not yet fully understood, SGs are implicated as temporary storage sites of mRNAs and proteins, signalling hubs, and as mediators of translation control. Emerging evidence suggests SGs also play a role in protein aggregation [22–24]. Given that SGs can form as a part of the stress response and SG-

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like foci are observed in tissues under pathological contexts [25–28], they may play a protective or detrimental role in cellular health [29]. The dynamic assembly and disassembly of SGs is likely important for their function, consistent with the defects in SG assembly and disassembly linked with genetic diseases [30]. For example, mutations in the genes encoding SG proteins, TIA-1 (T-cell intracellular antigen-1) and ANXA11 (annexin A11), are associated with ALS (amyotrophic lateral sclerosis) and FTD (frontotemporal dementia), and exogenous expression of these alleles delays SG disassembly during recovery from stress [31,32]. Additionally, inclusion bodies harbouring SG proteins are observed in neurodegeneration [25,26,33–35]. Therefore, defining the precise mechanisms of SG regulation and function holds promise for revealing fundamental mechanisms of gene expression, cell health, and disease.

Whether SG dysregulation causes or results from proteostasis collapse remains unresolved. Impaired SG assembly is associated with ageing and ALS in model organisms, suggesting SGs are protective [36–38]; consistent with this, overexpressing the SG nucleating protein G3BP1 (G3BP stress granule assembly factor 1) improves proteostasis and mitigates neurodegenerative phenotypes in spinocerebellar ataxia models [39]. Yet preventing SG formation can also alleviate disease-associated protein aggregation characteristic of neurodegenerative pathology in patient-derived cell lines and animal models, suggesting SGs are detrimental [40,41]. These opposing findings suggest SG dysregulation may be both a cause and a consequence of proteostasis collapse. Human genetics data reinforces the link between SGs and the proteostasis network, as variants in genes encoding proteostasis factors that influence SG dynamics are associated with disease [42–44]. Understanding the interplay of proteostasis and SGs may therefore yield fundamental insights into cellular function and disease mechanisms.

This review examines the bidirectional relationship between SGs and the proteostasis network (Figure 1). We first discuss how protein synthesis, quality control, and degradation factors regulate SG assembly, composition, dynamics, and disassembly. We then examine the emerging evidence that SGs in turn contribute to proteostasis by regulating translation, protein quality control, and protein aggregation.

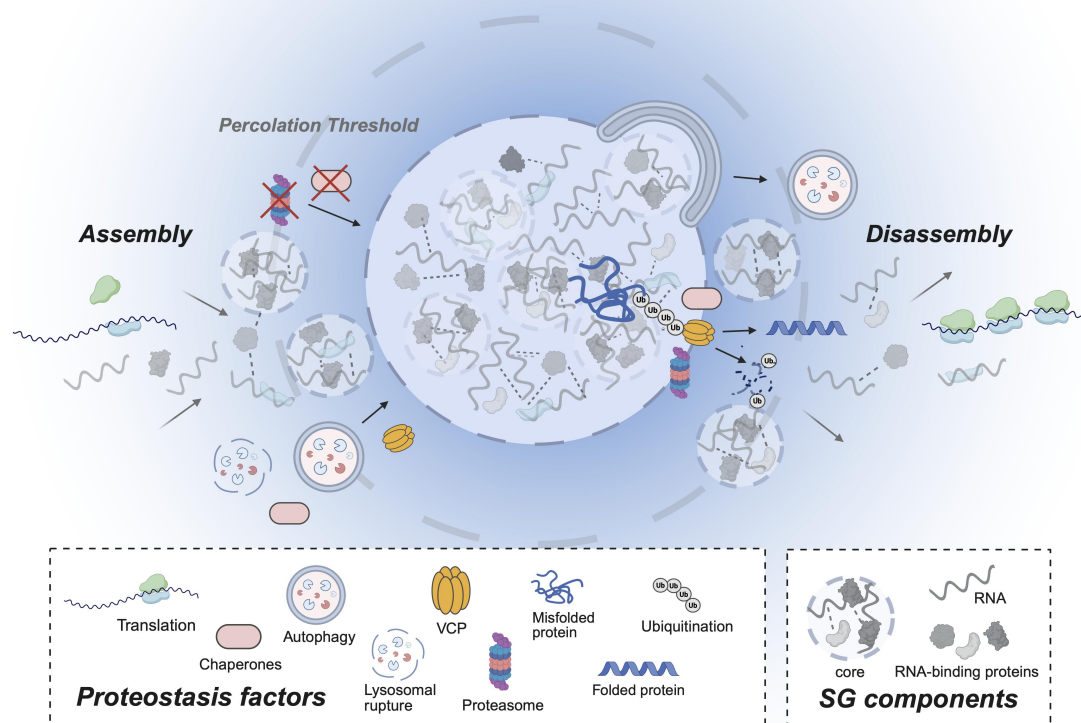


Figure 1. Stress granules intersect with the proteostasis network. The proteostasis machinery includes chaperones, translation factors, ubiquitin-proteasome system, and autophagy components. Proteostasis factors influence SG assembly, dynamics, and disassembly.

Viewing SGs as a functional node within the proteostasis network may clarify how their dysregulation contributes to neurodegeneration, cancer, and ageing.

The role of proteostasis machinery in stress granule assembly

Stress granules form through multivalent interactions of non-translating mRNAs with proteins and other RNAs when translation initiation is suppressed [19,45–47]. Translation initiation suppression canonically occurs through the integrated stress response (ISR), a signalling pathway activated by proteotoxic and other stresses, but it can also take place through ISR-independent mechanisms. The ISR is activated by any of four eIF2 α (eukaryotic initiation factor 2 α) kinases that phosphorylate eIF2 α (P-eIF2 α). P-eIF2 α inhibits eIF2B and limits the formation of ternary complexes, resulting in suppression of translation initiation [48,49]. The ISR inhibitor, ISRIB, which increases translation initiation activity during stress, inhibits SG formation in cells treated with arsenite or thapsigargin [50]. However, SGs can also form independently of P-eIF2 α when ribosome recruitment to mRNAs is inhibited, such as upon suppression of other eukaryotic initiation factors like eIF4A and eIF4G [51,52]. For example, pateamine A, hippuristanol, and hydrogen peroxide induce SGs by disrupting the eIF4F complex [52–54]. Therefore, inhibition of translation initiation, during the ISR or independently of it, is an important trigger of SG assembly.

Stress granule assembly depends on the phase separation of the SG interaction network from the cytosol. This occurs when translationally repressed mRNAs and interacting proteins condense to surpass the percolation threshold, or concentration threshold where enough interactions have formed to allow for liquid-liquid phase separation [19–21,47,55]. Several pieces of evidence demonstrate RNA mediates SG assembly, where non-translating mRNAs play a key role in seeding and stabilizing SGs. First, SG assembly is inhibited by trapping mRNAs in polysomes with translation elongation inhibitors [45,56]. Second, when RNases are activated prior to SG assembly, canonical SG formation is impaired [19,57]. Third, the transcriptomes of *in vitro* assembled RNA droplets and purified SGs from cells are very similar [46]. Finally, SGs harbour stable substructures assembled by RNA-RNA interactions that persist in the absence of the nucleating protein, G3BP1, *in vitro* and in U-2 OS cells [58,59]. Therefore, mRNA freed from the translating pool is critical for SG formation.

G3BP1 and its functionally redundant paralog G3BP2 (together, G3BP1/2) [60] are the most widely used markers for identifying SGs, as they localize to SGs across most stress conditions. Other canonical SG markers include TIA-1, UBAP2L (ubiquitin-associated protein 2-like), and PABP (poly(A) binding protein) [61,62]. Although G3BP1/2 are often described as SG scaffolds, SGs may be better described not as structures built on a fixed scaffold, but as networks of interactions that range from relatively stable to highly dynamic. The assembly of SGs occurs upon formation of biochemically purifiable, RNA-protein substructures called ‘cores’ of SGs, followed by progressive recruitment of additional stress-dependent interactors that form the less stable, liquid-like ‘shell’ [63]. While many RNA-binding proteins contribute to the SG interaction network, G3BP1/2 are widely considered critical SG assembly proteins because they are essential for SG assembly upon many, but not all stresses [16], yet G3BP1/2 are themselves highly dynamic within SGs. Single molecule tracking and fluorescence recovery after photobleaching (FRAP) of G3BP1/2 shows that, *in vivo*, G3BP1/2 are very dynamic within SGs and exhibit alternating states of fast (within the liquid phase of SGs) and transient immobile periods (associated with stable core regions of SGs) [55,64]. This dynamic state of G3BP1/2 contrasts with certain RNA molecules that have been shown to maintain a rigid position within SGs *in vivo* [65]. Additionally, the RNA within SGs forms a stable substructure that maintains SG integrity even in the absence of G3BP1 [19,58,66]. Thus, RNA may comprise the more stable structural element of SGs, rather than any single scaffolding protein. Multivalent G3BP1-RNA interactions drive separation and recruit other components [19–21]. Consistent with a distributed rather than scaffold-centred basis for assembly, SG formation can be driven by overexpression or multimerization of several RNA binding proteins in addition to G3BP1, including TIA-1, Caprin-1, and UBAP2L [16,61,67,62,68–70]. Additionally, TIA-1 knockout in mouse embryonic fibroblasts (MEFs) inhibits arsenite-induced SG formation [70], and SG assembly is impaired in yeast lacking the TIA-1 ortholog, Pub1, during glucose deprivation stress [67]. Overexpression of TIA-1 can rescue SGs to a limited extent when G3BP1/2 are knocked out [16]. Thus, multiple RNA-binding proteins can partially substitute for one another in SG assembly, reinforcing that SGs are better described as dynamic interaction networks than as fixed scaffolds.

Beyond G3BP1, SGs may also assemble around co-existing substructures such as distinct UBAP2L cores [19,62,71]. UBAP2L contributes to the SG network by interacting with G3BP1 and RNA. Mutagenesis of G3BP1 to disrupt binding to UBAP2L impairs the SG interaction network, demonstrating that the G3BP1-UBAP2L interaction is important for SG formation and/or stability [19]. Yet, UBAP2L depletion and knockout reduces, but does not abolish, SG formation across multiple stresses including arsenite, sorbitol, and hydrogen peroxide [19,20,30,71–73]. Thus, UBAP2L acts as a modulatory interactor rather than an essential nucleator [19,74]. Notably, UBAP2L connects the SG network to the ubiquitin-proteasome system: it has a ubiquitin-associated UBA domain and co-purifies with ubiquitinated protein aggregates, heat shock proteins, and p62 (sequestosome-1) from cells treated with proteasome inhibitors [75]. Similarly, the ubiquitin binding domain and deacetylase activity of the cytoplasmic HDAC6 (histone deacetylase 6) protein are required for arsenite-induced SG assembly in MEFs [76]. Therefore, ubiquitin-binding SG components such as UBAP2L may represent one route linking SG assembly to the ubiquitin-proteasome system.

Defects in proteostasis can trigger the ISR (reviewed in [49]) (Figure 2). Any of the four eIF2 α kinases can be activated upon proteostatic stress. The transmembrane stress sensor PERK (PKR-like endoplasmic reticulum kinase) is activated upon binding misfolded proteins that accumulate in the ER during the unfolded protein response (UPR) [77,78]. Defects in translation elongation that impact proteostasis by reducing protein synthesis rates, triggering ribosome collision, affecting co-translational folding, and producing aggregation-prone nascent chains activate GCN2 (general control non-derepressible 2) [79–82]. The ISR is also triggered when the proteasome is inhibited or downregulated through several proposed mechanisms. GCN2 or HRI (haem-regulated inhibitor) are required to activate the ISR in primary rodent neurons or MEF cells upon acute treatment with high levels of various proteasome inhibitors (e.g. MG-132,

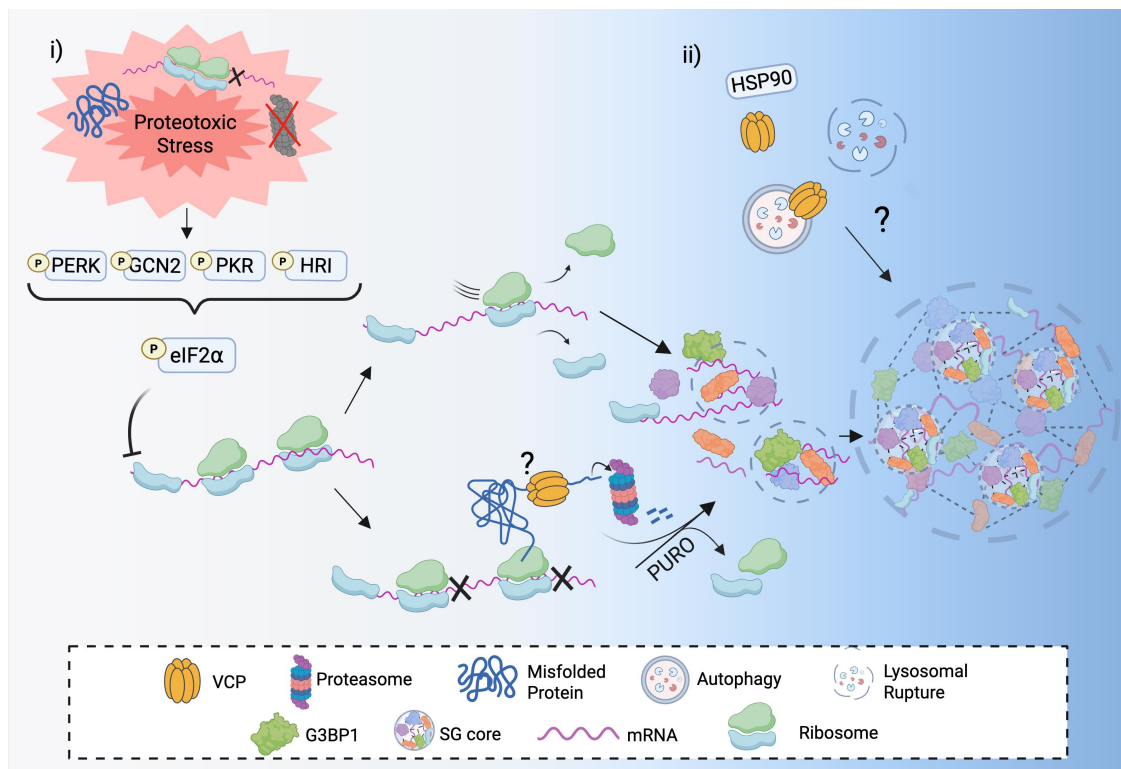


Figure 2. Stress granule assembly is regulated by proteostasis factors. (i) Proteotoxic stress can result in misfolded proteins, translation elongation defects, and/or other insults that cause phosphorylation of eIF2 α by PERK, GCN2, PKR, or HRI and activate the ISR. ISR activation inhibits translation initiation, and ribosomes run off the mRNA. In some cases (e.g. MG-132, VER-155008, arsenite, or heat), ribosome stalling may prevent the release of mRNAs from polysomes. Puromycin ("PURO") or the stress-activated RQC pathway resolve these stalls, promoting SG assembly. Freely available non-translating mRNAs condense and form a network containing enough protein-protein, RNA-RNA, and RNA-protein interactions to surpass the percolation threshold (blue gradient). (ii) Lysosomal damage, HSP90, and VCP activity also influence SG assembly.

lactacystin, or bortezomib) [83–85]. Further, depletion of subunits in a specialized form of the proteasome called the immunoproteasome triggers the ISR via PKR (protein kinase R) in a human monocyte model of proteasome-associated autoinflammatory syndrome (PRAAS) [86]. Therefore, impaired proteostasis is linked with activation of the ISR through diverse mechanisms.

Less is known regarding if or how defects in the UPS promote SG formation. Inhibiting the proteasome using MG-132 or lactacystin causes SG assembly in HeLa cells [22,87,88] (Figure 2). These SGs are likely induced via the ISR, as MG-132 reduces translation activity and does not induce SGs in cells expressing a non-phosphorylatable eIF2 α mutant [87]. The proteasome inhibitor bortezomib can also cause SG assembly, but this appears to occur in a cell type-dependent manner that is not understood [89]. Additionally, a later study found that MG-132 did not induce SGs in normal rat kidney (NRK) cells, unless they were co-treated with puromycin, an amino-acyl tRNA mimic that releases nascent proteins and mRNAs from elongating ribosomes [47,90]. Because puromycin treatment also restores SG assembly in stressed cells treated with tRNA synthetase inhibitors that block translation elongation [91], these results suggest that MG-132 prevents the release of mRNAs from polysomes in some, but not all, cell types. However, another possibility is that proteasome inhibition alone is not sufficient to induce high enough levels of P-eIF2 α to drive SG assembly under these conditions, but puromycin may further overload the UPS such that the ISR is robustly activated and SGs assemble. These two possibilities are not mutually exclusive and may depend on cell-type specific effects such as whether or not the ISR is activated; indeed, while MG-132 activates the ISR in HeLa cells [87], another study showed P-eIF2 α was not detectably increased in NRK cells upon MG-132 treatment, unlike arsenite stress [47].

Chaperones appear to be largely dispensable for SG assembly, although specific heat shock proteins (HSPs) may impact SG formation through indirect or context-specific effects. While formation of MG-132-induced SGs is unaffected by depletion, inhibition, or overexpression of chaperones HSPB8 or HSP70 or co-chaperone BAG3 (BCL2-associated athanogene 3) [23], another study found the HSP90 inhibitor 17-AAG indirectly impairs SG assembly by destabilizing an upstream signalling kinase, TBK1 (TANK-binding kinase 1), which is required for SG assembly through unclear mechanisms [92]. Results of one study indicate that inhibition of HSP70 with VER-155008 or quercetin induces SGs upon puromycin co-treatment in NRK cells, suggesting mRNAs remain associated with polysomes and cannot drive SG assembly when HSP70 is inhibited [47] (Figure 2). In line with this idea, HSP70 inhibition causes ribosome pausing, suggesting translation elongation inhibition [93]. However, VER-155008 does not inhibit SG assembly during arsenite stress in HeLa cells and instead causes a slight but significant increase in SG size [94]. Future work is needed to clarify whether and how chaperones influence SG formation.

Another key proteostasis factor, VCP (valosin-containing protein), may promote SG assembly through several mechanisms. VCP is a hexameric AAA+ ATPase that extracts and unfolds ubiquitinated proteins from membranes and complexes for subsequent degradation by the proteasome or autophagy. First, knockdown of VCP by siRNA or VCP inhibition results in accumulation of ubiquitinated proteins and also causes smaller, ‘dispersed’ MG-132- and arsenite- induced SGs to assemble, suggesting that VCP-mediated protein remodelling or clearance is required for proper SG assembly [88]. Depletion of VCP co-factors PLAA (phospholipase A2-activating protein) or UFD1L (ubiquitin fusion degradation 1 like) similarly reduces SG formation [88]. Second, VCP depletion leads to accumulation of LC3-II, suggesting autophagy is activated [88]. Because autophagy may promote SG clearance [95], one possibility is that VCP inhibition reduces SGs in cells by activating autophagy. Third, chemical inhibition of VCP also reduces the localization of several mRNAs to SGs [96]. Interestingly, treatment with puromycin rescues the recruitment of these mRNAs to SGs when VCP is inhibited, suggesting that these mRNAs are trapped within polysomes when VCP is inhibited during stress [96]. VCP may thus promote SG assembly indirectly through protein quality control activities and by resolving ribosomal stalls to allow release of trapped mRNAs into the translating pool during stress (Figure 2).

Finally, inhibition of autophagy and lysosome function also impacts SG assembly through unclear and contradictory molecular mechanisms (Figure 2). Deletions in autophagy genes cause increased constitutive SGs in baker’s yeast in the absence of stress [95]. Additionally, homozygous deletion of *Atg7* and *Atg3* in MEFs also causes SGs to form in some cells [95]. In contrast, depletion of *Atg5*, *Atg16*, or other autophagy factors in MEFs or human FaDu cells reduces SG formation upon arsenite or MG-132 stress [88,92]. Similarly, lysosomal inhibition by ammonium chloride or chloroquine reduces the size of arsenite-, MG-

132-, or heat-induced SGs [88] or inhibits them from forming [92]. However, lysosomal damage can also induce SG assembly [97], SGs can associate with lysosomes [98], and SGs may assemble at lysosomal membrane ruptures [99]. Further research interrogating mechanisms by which UPS and autophagy regulate SG assembly may clarify these contrasting results and shed light on how defects in protein degradation are sensed and resolved in the cell.

Proteostasis and stress granule properties

Stress granule properties can be characterized by their composition (the proteins and RNAs that constitute SGs) and dynamicity (whether SGs exhibit dynamic, 'liquid-like' behaviour or more stable, 'solid-like' interactions). Stress granules harbour proteostasis factors and are potential sites of proteostasis activities that impact SG dynamicity.

Stress granules contain a conserved set of defining components, such as G3BP1/2 and RNA, in addition to recruiting 'client' proteins and RNAs in a context-specific manner [19–21,100] (Figure 3). The RNA binding proteins G3BP1, poly(A)-binding protein (PABP1), and the translation initiation factors eIF4G and

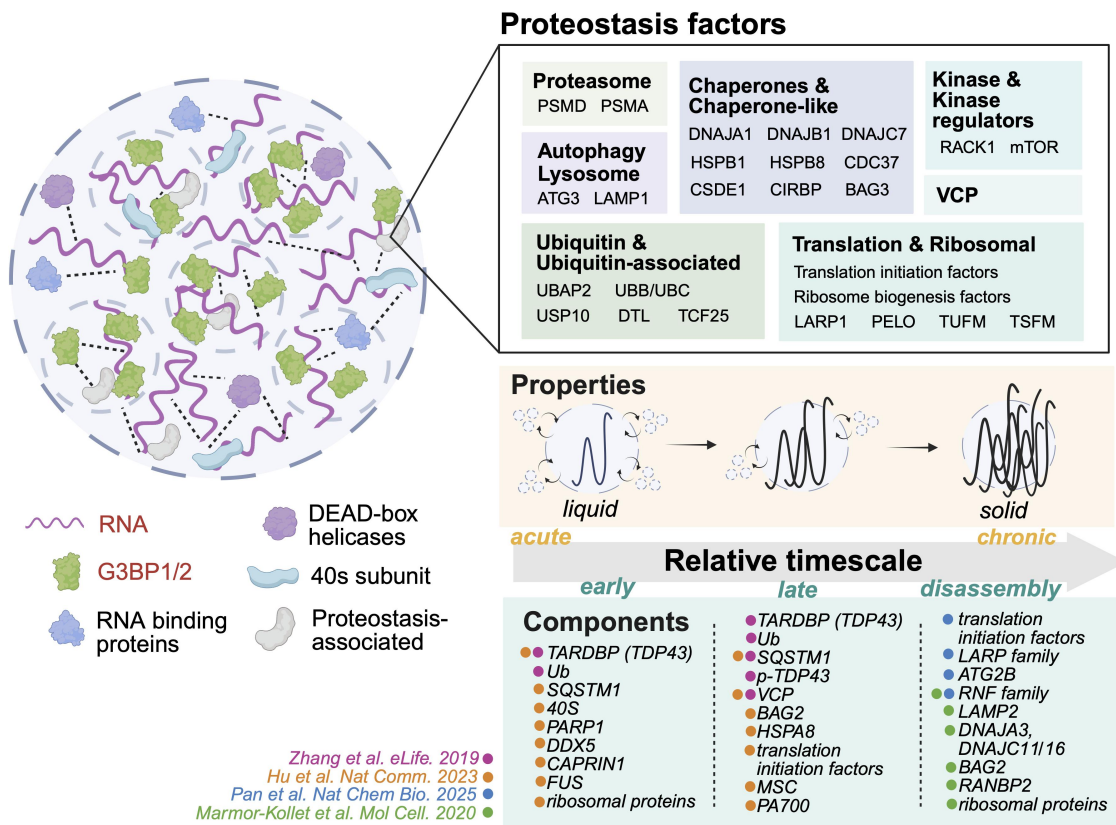


Figure 3. The composition and properties of stress granules are diverse, intersect with proteostasis, and change by timescale. Critical SG biomolecules, G3BP1 and mRNA (red font) and various RNA-binding proteins, helicases, translation factors and other proteostasis components, are among the diverse components associated with SGs. ~18% of SG-associated genes in the RNA granule database functionally annotated are associated with the proteostasis network (Millar et al. [104], Huang et al. [114], Sherman et al. [115]). *In vitro* reconstituted assays of liquid-liquid phase separation of biomolecules, optogenetics-induced SGs, and accumulating misfolding-prone proteins in SGs have suggested a liquid to solid-like transition with time. Timescale studies of SG composition have shown differing SG components in early, late and disassembly stages. Data were derived from the four indicated studies. Proteins identified in Zhang et al. [69] are indicated by red dots, with 'early' defined as presence in SGs in at least 20% of cells within 1 hr and 'late' as after 1 hr. SG proteins identified in Hu et al. [111] are marked with orange dots, with 'early' as proteins primarily enriched in SGs within 20 min, and 'late' as proteins primarily enriched in SGs after 30 min. Proteins identified in Pan et al. [113] are indicated with blue dots and were identified during SG disassembly at least 30 min after removal of arsenite stress. Proteins identified by Marmor-Kollet et al. [103] are indicated with green dots and were identified during SG disassembly at least 30 min after arsenite removal.

eIF3 are unique to SGs and not other RNP (ribonucleoprotein) granules [61]. A common SG proteome that includes key proteins is observed across diverse contexts. An immunofluorescence screen in arsenite-stressed cells identified ~55% (42/77) of human RNA binding proteins (RBPs) present in SGs in HepG2, Hela, and neuroprogenitor (NPC) cell lines [101]. Further, 77% (40/52) of assayed RBPs localize to SGs in both arsenite and heat stress within Hela cells, and G3BP1-APEX- based mass spectrometry experiments show 54% (96/178) of proteins in NPCs are shared SG components across arsenite and thapsigargin stress [101]. The SG proteome under arsenite stress also contains ribosomal subunits and other translation factors, ATPases such as DNA/RNA helicases (e.g. the MCM complex, RuvBI complex, DEAD-box proteins) and heat shock proteins in yeast and U-2 OS cells [102]. Additionally, proteins enriched in SGs more frequently harbour intrinsically disordered regions (IDRs) compared to the total cell proteome [71,103]. An online RNA granule database provides a curated list of proteins observed in SGs in mammalian cells across 220 studies, inclusive of SG networks found in unstressed and stressed, such as arsenite and heat shock, conditions [104]. Although variation in the SG proteome is observed depending on stress, cell type, or technique [71,101,103,105], SGs generally harbour a shared subset of protein components that includes proteostasis factors.

RNA also forms stable core substructures in SGs [58,102]. Super-resolution imaging and biochemical assays show SGs have stable RNA and protein ‘core’ substructures encompassed by dynamic ‘shells’ in yeast and mammalian cells under arsenite stress [62,64,102,103]. Single molecule imaging experiments reveal protein and RNA molecules interact either dynamically or stably with SGs, suggestive that these components partition into ‘core’ or ‘shell’ compartments [64,65,106]. Stress granules harbour translationally repressed mRNAs (estimated at ~10% of bulk mRNA in the cell), long non-coding RNAs, and are enriched in longer RNAs and mRNAs with low translational efficiency [65,106–109]. Furthermore, like the SG proteome, the RNA composition of SGs can differ by context: ~38% (688/1816), ~40% (757/1871), and ~53% (1155/2191) of arsenite-induced SG transcripts in SK-N-BE, U-2 OS, and SMMC-7721 cell lines are unique to the cell type, respectively [110]. The SG transcriptome may also change within disease contexts. For example, overexpression of a disease-associated FUS (fused in sarcoma) (P525L) mutant leads to SG transcriptome changes including increased localization of AU-rich and less structured transcripts to SGs [110].

Time-resolved proteomics and immunofluorescence imaging of G3BP1 or other SG protein interactomes have shown that SG composition is dynamic over time (Figure 3). For example, proteomics of heat-stressed U-2 OS cells across a 180 min time course revealed early stage SG components (enriched in SGs in the first 20 min of stress) are enriched in proteins with IDRs, proteins implicated in SG nucleation, and RNA metabolism proteins, reinforcing that protein-RNA interactions and the principles of phase separation promote SG assembly [111]. Late stage-SG proteins (increasing in SGs after 30 min of stress) include VCP, subunits of the 19S proteasome regulatory particle, the multi-tRNA synthetase complex (MSC), other translation factors such as eIF3, and mediators of protein transport [111]. These changes may be conserved, as SGs in baker’s yeast during heat stress similarly recruit tRNA synthetases and eIF3 [112]. Other time-course studies have also shown SGs dynamically change composition over time. Stress granules induced by optogenetic multimerization of G3BP1 (‘optogranules’) that persist for at least 5 hours exhibit differential accumulation of proteins over time as measured by immunofluorescence microscopy [69]. Further, the interactomes of G3BP1 and FMR1 (fragile X messenger ribonucleoprotein 1) when SGs disassemble after arsenite removal show additional translation and protein quality control factors including proteins involved in ubiquitination and autophagy are recruited to them (Figure 3) [69,103,113]. Therefore, while core components are present across conditions, the protein composition of SGs can change over time.

Proteostasis factors are also recruited to SGs in association with misfolded, aggregation-prone proteins. These proteostatic mediators likely promote SG dynamicity and may facilitate refolding, release, or degradation of misfolded, aggregation-prone proteins. Functional annotation [114,115] of the SG components in the RNA granule database (Tier 1 proteins) [104] reveals at least ~18% of the SG proteome of human cell lines within SG networks found in unstressed, arsenite, and heat shock conditions are proteostasis factors, including chaperones (e.g. HSP60, HSPB1), ubiquitin-associated proteins (e.g. UBAP2L, UBAP2), translation factors, kinases and their regulators (e.g. RACK1), and ribosomal subunits (Figure 3). Proteostasis factors not only localize to SGs, but also likely impact SG properties. For example, knockdown of ZFAND1 (zinc finger AN1-type containing 1) leads to SG persistence and reduces

proteasome and VCP localization to SGs in arsenite stress [116]. Inhibition of the HSP70 chaperone with VER-155008 increases the abundance of aberrant SGs containing misfolded protein constructs and poly-ubiquitin under heat stress [22]. Therefore, proteostasis factors make up a substantive portion of the SG proteome and actively impact SG properties.

The observations that SGs accumulate aggregation-prone proteins suggests they serve as hubs or triage areas for protein degradation, storage, or refolding. Misfolded proteins and defective ribosomal products (DRiPs; partially formed polypeptides released or extracted from ribosomes with the potential to aggregate) localize to SGs [22,116]. While DRiPs are typically degraded through the UPS [117], inhibition or depletion of VCP, ZFAND1, PLAA, or UFD1L under arsenite stress, or the HSPB8-BAG3-HSP70 complex under proteasome inhibition by MG-132, increases their localization to SGs [23,88,116]. Mutant SOD1 (superoxide dismutase 1) proteins associated with disease that have poor folding stability in cells are also more likely to localize to SGs under heat stress over time in comparison to wild-type SOD1 proteins [22]. Inhibiting HSP70 activity or depleting the co-chaperone, DNAJB1, increases accumulation of pre-amyloid structures in SGs [94]. Optogranules induced by G3BP1 multimerization also recruit ubiquitin, VCP, p62, and proteins such as TDP-43 (transactive response DNA-binding protein of 43 kDa) that are found in neurodegeneration-associated inclusion bodies over time [69]. Finally, limiting ATP generation with glycolysis and/or oxidative phosphorylation inhibitors reduces SG dynamicity, perhaps by suppressing the activity of ATP-dependent UPS factors including VCP or chaperones [55,102].

SGs can become more stable and lose dynamicity over time, suggesting proteostatic processes that refold or clear protein aggregates may be overwhelmed within SGs or lose activity during prolonged stress (Figure 3). Within reconstituted G3BP1-RNA condensates *in vitro*, a temperature-dependent destabilized protein reporter prone to misfolding (Ubc9(ts)) becomes less mobile over time [21]. Furthermore, *in vitro* condensates themselves become less dynamic, exhibiting slower fusion times than those harbouring stable, wild-type Ubc9 [21]. Numerous *in vitro* studies of RNP granule components demonstrate protein and RNA-protein condensates can transition over time from dynamic to stable assemblies including fibrils, suggesting SGs could evolve into pathological aggregates [118–120]. In cells, optogranules in the absence of stress become more stable with time as they accumulate ubiquitin and UPS factors [69]. Further, SGs that harbour misfolded protein reporters are less dynamic and recruit heat shock proteins, poly-ubiquitin, and VCP under heat stress [22]. Therefore, while SGs may be storage and/or triage sites for aberrant proteins targeted for degradation, aberrant maintenance and accumulation of aggregation-prone proteins may change the properties of SGs, impairing their dynamicity.

Proteostasis factors regulate SG disassembly

SG disassembly occurs when the interaction network between core components falls below the percolation threshold when stress is resolved as cells adapt and recover translation activity. Research largely based on live-cell imaging during recovery from arsenite stress suggests a model wherein the dynamic, liquid-like ‘shell’ of SGs is cleared first as weakly associated mRNPs (messenger ribonucleoproteins) exchange back into the recovering translational pool, with the more stable ‘cores’ disassembling or undergoing degradation through ATP-dependent remodelling complexes (e.g. HSP70, VCP, and RNA helicases) and the UPS and autophagy second [59,63,121] (Figure 4). In line with this model, a proximity-labelling transcriptomics approach during and after acute arsenite stress revealed that mRNAs that exit SGs earlier during the SG disassembly process have higher translational efficiency than mRNAs that exit SGs later [109]. Further, using cycloheximide or emetine, which trap mRNAs in polysomes and deplete the free mRNA pool, causes SG disassembly [45,56,122]. Additionally, ISRIB and DNL343, which cause translation reinitiation during stress by increasing eIF2B activity when eIF2 α is phosphorylated, also drive disassembly of preformed arsenite- or thapsigargin- induced SGs [50,123]. Therefore, restoring translation initiation actively drives SG disassembly.

Molecular chaperones including HSPs that refold or target misfolded proteins for degradation localize to SGs, where they likely indirectly promote SG disassembly by clearing misfolded proteins that would otherwise stabilize the granules [101,102,104,111,124]. HSP72 depletion or HSP70 inhibition with VER-155008 prevents or delays SG disassembly after heat, oxidative, hyperosmotic, or proteasome inhibition (MG-132) stress in HeLa cells [22,52,87,94]. Similarly, SGs persist in yeast expressing a dominant negative Hsp70 allele or depleted of Hsp40 proteins after sodium azide stress, demonstrating they are involved in SG disassembly [124,125]. The severity of

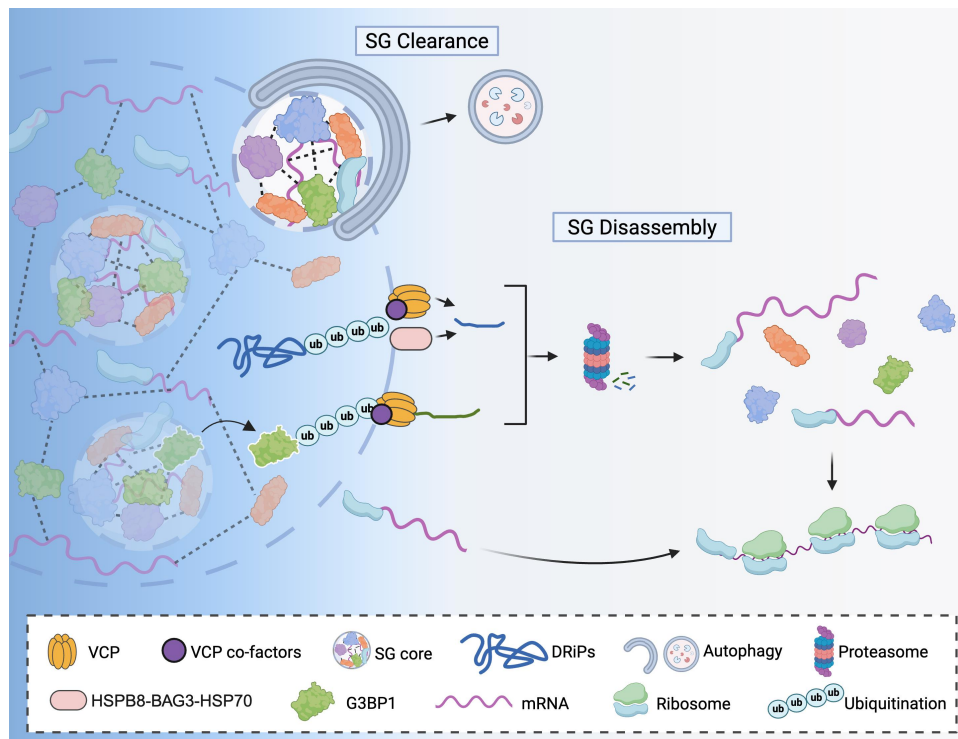


Figure 4. Stress granule disassembly is regulated by proteostasis factors. As stress is removed or cells adapt to stress, SGs disassemble when the SG interaction network falls below the percolation threshold (blue gradient). Stress granules can disassemble as translation recovers, be cleared by autophagy or proteasome activity, and can be remodelled to re-enter translation. Stress granules can also be disassembled, which is mediated by translation activity, chaperones (e.g. HSPB8-BAG3-HSP70), and protein degradation factors. These activities and factors release mRNAs or ubiquitinated (e.g. G3BP1) or misfolded proteins/DRiPs from SGs and promote SG disassembly as component interactions drop below the percolation threshold (blue gradient).

the stress could impact the effect of HSP70 inhibition, as the duration of SG persistence after stress upon VER-15508 treatment correlates with the concentration of arsenite in HeLa cells [94]. Additionally, the HSPB8-BAG3-HSP70 complex prevents DRiPs and unfolded protein reporters from accumulating in SGs and may thus indirectly stabilize SGs during proteasomal suppression with MG-132 in human cells [23] (Figure 4). Because small HSPs can assist HSP70 in refolding or targeting misfolded proteins for degradation [126,127], together these results suggest multiple HSPs aid in SG disassembly as a consequence of targeting aggregation-prone, misfolded proteins within them. Notably, while active HSP70 is important for SG disassembly, it is not required for its recruitment into arsenite-induced SGs, since both an ATPase-inactive HSP70 variant and endogenous HSP70 treated with VER-155008 were enriched in SGs as in wildtype, untreated HeLa cells [94]. Restoration of translation was also delayed when inhibition or depletion of HSPs caused persistent SGs induced by MG-132, suggesting chaperone-mediated clearance of SGs is important for protein synthesis to recover after stress [23,124]. Although many chaperones are constitutively expressed in unstressed cells to maintain normal proteostasis, stress can trigger activation of the transcription factor heat shock factor 1 (HSF1). HSF1 upregulates HSP72 and HSP27, as seen during prolonged, low dose arsenite stress in cultured astrocytes or under high concentrations of arsenite for shorter time periods in neuroblastoma cells [128,129]. Stress-induced HSP upregulation may help promote timely SG disassembly and recovery from stress.

Ubiquitination of SG components is also required for their disassembly in a stress-specific manner. Following heat stress, ubiquitination of the NTF2L (nuclear transport factor 2-like) domain of G3BP1 is important for heat-induced SG disassembly or clearance, as a G3BP1 mutant that cannot be ubiquitinated causes delayed SG disassembly during the recovery phase in U-2 OS cells [55] (Figure 4). Consistent with this finding, blocking ubiquitination by the UBA1 (ubiquitin-like modifier-activating enzyme 1) inhibitor TAK-243 delays SG disassembly during recovery from heat stress in U-2 OS cells [55,130], and to a lesser extent following arsenite stress in HeLa cells [131,132]. However, other studies found pre-treatment with TAK-243 has no effect on arsenite-induced

SG disassembly in HCT116 cells, and mono-ubiquitin, but not poly-ubiquitin bound to proteins, accumulates in arsenite-induced SGs [133]. The stress-dependent context of the requirement for ubiquitination during SG disassembly could be due to differences in the ubiquitination pathways engaged by different stresses and/or different cell types. In support of this idea, several RNA-binding RING-type ubiquitin E3 ligases including MKRN2 (makorin ring-finger protein 2), CNOT4 (CCR4-NOT transcription complex subunit 4), TRIM25 (tripartite motif-containing 25), and ZNF598 (zinc finger protein 598) are associated with heat-induced SGs in U-2 OS cells [130], while HECT-domain E3 ligases are enriched in arsenite-induced SGs in HEK293T cells [113]. In contrast to the stress-specificity of ubiquitination in SG clearance, SUMOylation promotes SG disassembly following both arsenite and heat stress, as depletion of the SUMO-dependent ubiquitin ligase RNF4 or SUMO2/3 delays SG clearance [134]. Ubiquitination may thus promote disassembly by marking SG proteins for extraction by segregases such as VCP or for degradation through the UPS or autophagy. Whether this requirement for ubiquitination is truly stress-specific or also reflects differences between cell types remains unclear.

VCP promotes SG disassembly after heat or arsenite stress, as inhibition or depletion of VCP delays SG clearance [55,95,116,131,135,136] (Figure 4). The VCP cofactor FAF2 (FAS-associated factor 2) was identified as a key mediator of heat-induced SG disassembly in U-2 OS cells, as it localizes to SGs, it interacts with G3BP1 in a ubiquitin-dependent fashion during heat stress, and SG disassembly is delayed when it is depleted [55]. Phosphorylation of VCP by ULK1 and ULK2 (unc-51-like autophagy activating kinase 1 and 2) is also implicated in activating VCP and promoting SG clearance, as chemical inhibitors of these kinases delay clearance of heat- and arsenite-induced SGs in U-2 OS cells [137]. The VCP- and proteasome-interacting protein ZFAND1 is implicated in arsenite-induced SG disassembly in Hela cells, but not for heat or osmotic stress [116]. Knockout or siRNA depletion of ZFAND1 leads to persistent SGs after arsenite removal compared to control cells [116]. Additionally, proteomics analysis of arsenite-induced SGs demonstrated TAK-243 treatment reduces VCP and ubiquitin in SGs in HEK293T cells, suggesting that VCP could be recruited to SG in a ubiquitin-dependent manner [113]. Stress-specific cofactors may therefore target VCP to release proteins from SGs for their degradation by the proteasome or autophagy pathways.

Protein degradation through the UPS or via autophagy is also implicated in SG clearance. Inhibiting the proteasome with bortezomib blocks arsenite- or heat-induced SGs from being disassembled or cleared in Hela cells [116,131]. Further, autophagy factors also aid SG clearance (Figure 4). A microscopy-based screen of nonessential gene deletions revealed autophagy aids SG turnover in baker's yeast [95]. Deletion strains (including *atg8Δ*, *atg11Δ*) exhibit constitutive SGs, and SG proteins accumulate in intravacuolar compartments in strains (e.g. *atg15Δ*) with impaired autophagic vesicle dissolution [95]. Similarly, a subset of *Atg3*- and *Atg7*-deficient MEFs have constitutive SGs and *Atg7*-deficient MEFs have delayed heat-induced SG clearance compared to wild-type cells [95] and lysosome or autophagy inhibitors delay SG clearance after stress [23]. Intriguingly, autophagy may play a greater role in SG clearance after prolonged stress, as increasing heat stress duration is associated with a greater defect in SG clearance in cells treated with the autophagy inhibitor bafilomycin A1 [55]. The mechanism of SG disassembly may depend on the duration and type of stress, the specific cell system, and dictate whether the components of SGs are recycled or degraded.

Proposed stress granule functions intersect with the proteostasis network

The function of SGs is a growing area of research. Stress granules may serve beneficial roles during stress as cell signalling hubs, translational suppressors, mediators of protein quality control of ribosomes, nascent polypeptides, and misfolded proteins, and interactors of other proteostasis-implicated biomolecular condensates. Stress granule interaction networks pre-exist at baseline [71,101,109,111], potentially priming the cell to rapidly escalate and de-escalate the cellular response to stress and maintain proteostasis. However, SGs may be harmful: SGs may seed the assembly of pathological disease aggregates [24], and persistent SGs, such as those modelled by optogranules, accumulate disease-associated inclusion body markers including ubiquitinated proteins [69]. Thus, SG dysregulation and their intersection with the proteostasis network could alter the proteostatic balance and cellular fate.

Stress granules may function as signalling hubs that impact cell survival during stress (reviewed in [138]). Inhibiting SG assembly via G3BP1/2 knockout or ISRIB increases caspase cleavage and apoptosis during stress, suggesting SGs suppress pro-death signalling [139]. Consistent with this, executioner caspases, caspase-3 and caspase-7, are localized to SGs induced by arsenite, selenite, or thapsigargin stress [139]. Stress granules may

similarly modulate growth signalling. mTORC pathway-associated proteins, such as mTOR, RAPTOR, astrin, S6K1, and S6K2, localize to SGs formed under arsenite stress, osmotic stress, and eIF4A inhibition [140,141]. Furthermore, proper SG regulation by proteostasis factors may impact SG-mediated signalling. Inhibiting ATPase activity of the chaperone, HSP90, delays release of Raptor from SGs, which may indirectly suppress mTORC1 activity and the resumption of translation after arsenite stress [142]. Thus, SGs and their potential regulation by proteostasis factors may modulate cell signalling through the sequestration of signalling factors (Figure 5).

Stress granules could also serve a protective role by suppressing translation during stress (reviewed in [18]) (Figure 5). Briefly, transcriptome- and proteome-wide analyses [107,108,143] and single mRNA imaging experiments [65,96,144] demonstrate that mRNAs sequestered in SGs are translationally repressed. Release of mRNAs from ribosomes is a prerequisite for their assembly into SGs [45,65,144], as few as one ribosome associated with an mRNA can inhibit mRNA localization to SGs [144], and trapping all mRNAs in monosomes inhibits SG assembly [144]. mRNA elements that promote translation of stress-induced genes during stress called upstream open reading frames (uORFs) inhibit mRNA localization to SGs by recruiting ribosomes [144], although reporter mRNAs containing the ATF4 (activating transcription factor 4, a stress-induced gene) uORF show increasing nascent protein signal within SGs over time in rare instances [145]. Because translating mRNAs interact with SGs only transiently [65], these rare events likely reflect transient association rather than sustained translation within granules. Thus, SGs sequester mRNA transcripts away from the translational machinery, which may prioritize the translation of stress-induced genes that are vital for the adaptation to, or recovery from, stress.

Stress granules may play a role in protein, mRNA, and ribosome-associated quality control pathways (Figure 5). First, USP10 (ubiquitin-specific peptidase 10) links SGs to 40S ribosome recycling. USP10 is a deubiquitinase that blocks SG assembly by binding to G3BP1 and outcompeting interactions with other RNA binding proteins to limit higher order network assembly under arsenite, patemamine A, and clotrimazole treatment [16]. The G3BP1-USP10 complex also deubiquitinates ubiquitinated 40S subunits for their

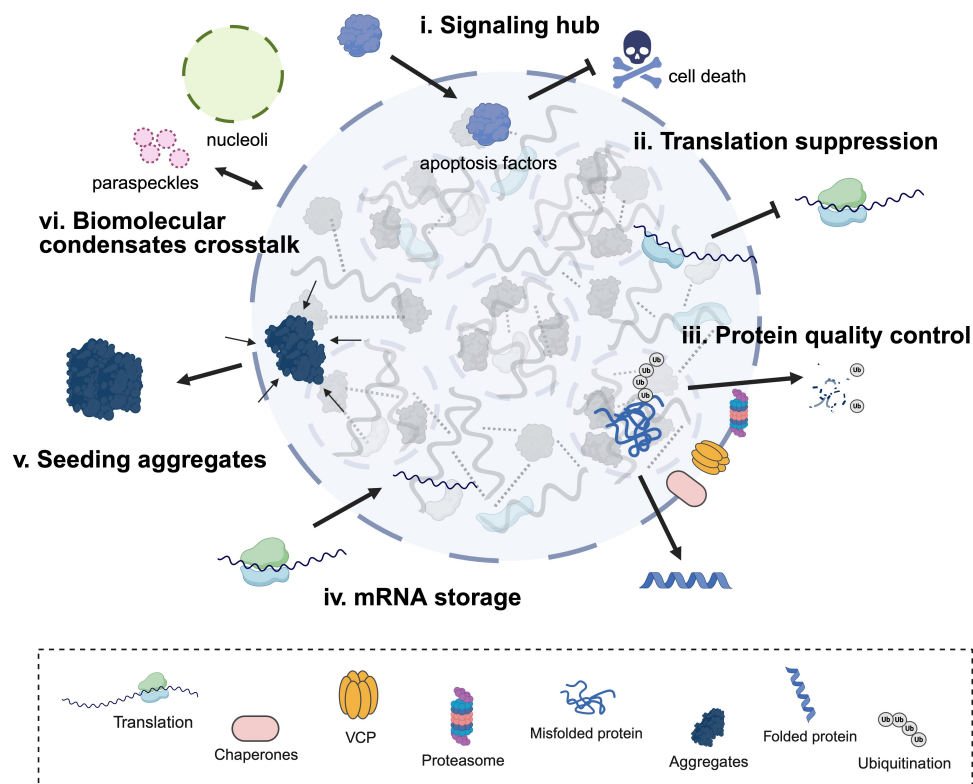


Figure 5. Potential stress granule functions intersect with the proteostasis network. Stress granules may play beneficial or detrimental roles for cellular resilience to stress, such as i) serving as signalling hubs and preventing apoptosis; ii) suppressing translation by sequestering mRNAs; iii) facilitating protein quality control by harbouring the proteasome, chaperones, and VCP, and their substrates; iv) mediating mRNA storage after targeting by the stress-activated RQC; v) preventing or seeding protein aggregates; and vi) undergoing crosstalk with other biomolecular condensates.

recycling during ribosome-associated quality control (RQC) or initiation RQC [146,147]. Therefore, USP10 may promote translation activity through ribosome recycling in addition to blocking G3BP1 interactions with other SG components to suppress SG assembly. Second, SGs could be triage/storage sites of mRNAs that are released from stalled ribosomes in the stress-activated RQC pathway in arsenite and heat, but not ER-stressed cells [96]. Such mRNAs may be marked as aberrant and stored in SGs, where they may be triaged for re-entry into translation or degradation. Finally, SGs recruit DRiPs, misfolded proteins, and protein quality control machinery, such as chaperones, VCP, and poly-ubiquitin, suggesting they are protein quality control hubs [22,23]. As discussed in prior sections, for example, the inhibition and/or depletion of chaperones and co-chaperones impacts SG disassembly and the accumulation of misfolded proteins and DRiPs within SGs [22,23,87,94,148].

SGs intersect with other biomolecular condensates involved in proteostasis, through shared components, buffering of proteostatic load, and by reciprocally influencing their assembly. Shared protein components of nucleoli and SGs include FMR1 and FXR1 (fragile X-related protein 1) [19,103], SGNP (stress granule and nucleolar protein) [149], and SERBP1 (SERPINE1 mRNA binding protein 1) [150]. Further, nucleolar proteins (such as fibrillarin, NOP58, DDX21) can co-purify with SG cores [102], and have been identified in proximity labelling experiments [103]. Cross-talk between condensates, including P-bodies [61,65] and p62-associated condensates [151,152], is an active area of study [153]; here, we focus on nuclear condensates linked to proteostasis.

Stress granules have been implicated in buffering of nuclear proteostasis mediated by the nucleolus and PML (promyelocytic leukemia) bodies. The nucleolus is a hub of ribosome biogenesis and a misfolded protein depot [154] and PML bodies are involved in ubiquitylating SUMOylated misfolded proteins for degradation [155]. Stress granules may protect these nuclear compartments by sequestering DRiPs and other misfolded proteins in the cytoplasm. For example, G3BP1/2 depletion increases the accumulation of DRiPs and a UPS reporter substrate in nucleoli, increases PML bodies, and hyper-activates the SUMO-ubiquitin-RNF4 pathway (or StUbL, the SUMO-targeted ubiquitin ligase pathway) under heat stress [156,157]. When DRiPs and misfolded proteins in PML bodies and nucleoli are not cleared, they can transition to less dynamic, amyloid-like states [154,156]. This relationship is reciprocal: the StUbL pathway and PML body formation in turn promote proper SG disassembly [134].

Stress granules also share components with paraspeckles, and may regulate their assembly through sequestration of certain proteins. Paraspeckles are nuclear condensates scaffolded by the long noncoding RNA, *NEAT1* (nuclear paraspeckle assembly transcript 1) that regulate gene expression by sequestering proteins and RNA [158–161]. During stress, paraspeckles hyper-assemble in tandem with SG formation, and SGs may promote this hyperassembly by sequestering negative regulators of paraspeckle formation, most notably the cytoplasmic protein UBAP2L, thereby relieving their inhibitory effect [35]. TDP-43, another protein that inhibits paraspeckle assembly [35,158], partitions between nuclear paraspeckles and cytoplasmic SGs in a manner that may depend, in part, on its interactions with *NEAT1* [158,162]. A mutant TDP-43 (D169G) with impaired *NEAT1* binding exhibits increased assembly into SGs [162]. Because this mutation is linked with ALS, the partitioning of TDP-43 into paraspeckles and SGs may connect condensate cross-talk to disease.

Stress granules and degenerative disease

Impaired SG regulation could also lead to aberrant SG properties and persistence linked to numerous diseases, such as cancer [163], neurodevelopmental disorders [30], and neurodegenerative diseases [27,28]. We briefly discuss the intersection of SGs with ALS/FTD. Stress granule components are associated with inclusions in spinal cord, hippocampal, and frontal cortex tissues of ALS/FTD patients [25,26,33–35]. Furthermore, the markers of ISR activation are present in ALS patient samples [123,164]. Stress granules may seed disease-relevant pathological aggregates and inclusion bodies, and have been implicated in the aggregation of ALS/FTD-associated RNA-binding proteins containing low-complexity domains with phase separation properties, of which we focus on TDP-43 and FUS [118,165,166] (Figure 5).

TDP-43 is a predominantly nuclear RNA-binding protein found in cytoplasmic and nuclear aggregates in post-mortem pathology [167,168]. Wild-type and mutant TDP-43 (including ALS/FTD-associated *TARDBP* mutations in the low complexity, glycine-rich C-terminal domain such as A382T and G348C) have been found to co-localize with, accumulate within, and/or impact dynamics of SGs [25,31,38,169–174]. Stress granules have

been implicated in increasing the local concentration of TDP-43, promoting its aggregation [24]. Additionally, inhibition of the ISR slows or partially ameliorates pathology in mouse and fly models of ALS [26,123] while blocking the assembly of SGs harbouring cytoplasmic TDP-43 under arsenite stress [123]. However, the role of SGs in TDP-43 aggregation is not clear. While TDP-43 aggregates in ALS/FTD patient spinal cord and frontal cortex samples have been shown to colocalize with SG components [25,34], other studies found TDP-43 does not colocalize with SGs in spinal cord samples [170,175,176]. Optogenetics-mediated TDP-43 oligomerization, single particle tracking of TDP-43 under arsenite stress, overexpression of transfected TDP-43 constructs, or exposure of cells to sonicated fibrils have shown TDP-43 inclusions occur outside of arsenite-induced SGs [176–179]. Furthermore, TDP-43 localized to arsenite-induced SGs remains dynamic, while TDP-43 inclusions that form outside of SGs are stable [179]. Finally, an alphavirus-derived nsP3 protein that blocks SGs worsens disease phenotypes in ALS model systems [37], and SGs fail to form upon stress in a mouse model of ALS associated with TDP-43 mutations under hyperthermia conditions [36].

Stress granules have similarly been implicated in the phase separation and aggregation of FUS, another predominantly nuclear RBP found to mislocalize and aggregate in ALS/FTD [33,180,181]. FUS and FUS constructs harbouring disease-relevant mutations concentrated in the C-terminal RGG domains and the nuclear localization signal (e.g. R495X, R514G, P517L, R521G, and P525L) drive accumulation of FUS in the cytoplasm, where it can associate with SGs in cells and *in vivo* [169,182–189]. FUS partitioning into SGs is tuned by arginine methylation of the RGG domains. Methylated FUS reporters localize less efficiently to SGs than unmethylated FUS reporters, due in part to modulation of Transportin binding, which otherwise suppresses FUS condensation [190]. Consistent with an interaction with SGs, the interactome of mutant FUS (P525L) includes SG components (G3BP2, PABP1, Caprin-1 and HuR) even in unstressed cells [191], and FUS mutants linked with disease (R521C, P525L) increase SG number and size, and alter SG disassembly rates [169,192–194]. That the effect of FUS on SGs depends on its condensation is shown by a FUS mutant unable to undergo liquid-liquid phase separation, which fails to associate with, and instead blocks, SG assembly, possibly by sequestering SG assembly factors [182].

Whether SGs promote or protect against FUS aggregation remains unresolved. Stress granules may be sites of pathological transition: mutant FUS (R495X) can de-mix within SGs, a potential pathway to aggregation [24]. However, FUS aggregation may be independent of SGs. Mutant FUS (R521C, R522G, R495QfsX527, P525L, C-terminal truncations) spontaneously forms aggregates that are reported to variably colocalize with SG markers [183,195,196], and mutant FUS aggregate composition only partially overlaps with SGs [105,110]. Stress granules may be protective by limiting FUS aggregation. During stress, FUS mutants localize to SGs, and deletion of the FUS RNA-binding domains abrogates recruitment to SGs and promotes aggregation [197]. Thus, as with TDP-43, SGs may promote or limit FUS aggregation, depending on the context. Future studies clarifying how SGs interface with FUS and TDP-43 aggregation may illuminate disease mechanisms in these and other contexts.

Beyond TDP-43 and FUS, multiple genes implicated in ALS/FTD lie within the intersection of SG regulation, SG properties, and proteostasis, including expanded repeats in the *C9ORF72* gene [198] and in the *ATXN2* gene [199,200], and mutations in the *SQSTM1* (p62) [201–203], *SOD1* [204], *UBQLN2* [205,206], and *VCP* [43] genes. For example, *C9ORF72* repeat expression can trigger the ISR and SG assembly [207]. Further, SGs induced by toxic *C9ORF72* dipeptide repeat-containing proteins are less dynamic and are associated with prolonged translational suppression and increased cell death [208,209]. The *C9orf72* protein is also implicated in SG clearance by interacting with autophagy factors including p62, and depletion of either protein leads to persistent SGs after arsenite stress [201]. Similarly, *ATXN2* (ataxin 2) and constructs containing polyQ expansions in the *ATXN2* gene co-localize with SGs [41,210]. *ATXN2* levels affect SG dynamics, decrease TDP-43 recruitment to SGs, and impact expression levels of SG components (PABP1) [41,210]. Further, *VCP* regulates autophagy [211,212], and expression of disease-associated *VCP* alleles causes persistent SGs [55,95,135,136,213], TDP-43 mislocalization [95,212], and impaired autophagy [211,212]. Finally, *UBQLN2* (ubiquilin-2), linked to the ubiquitin-proteasome and autophagy-lysosome system, associates with SGs and disease-associated mutations may alter SG dynamics [44,214]. Further research into the molecular mechanisms linking SG defects and the proteostasis machinery to disease may suggest intervention strategies and lend insight into disease pathogenesis.

Conclusion

The intersection between SGs and the proteostasis network is a growing field of research that may clarify SG functions, how SGs act as a critical regulatory node in proteostasis, and the link between aberrant SGs and human

disease. Proper assembly, dynamicity, and disassembly of SGs require proteostasis and autophagy factors, and SGs in turn interface with the proteostasis network at multiple levels, including translation control, protein degradation, and aggregation, which are increasingly tied to ageing and disease. Defects in the UPS machinery or autophagy pathways can result in persistent, aberrant SGs, and the evolution of SGs over time may contribute to disease in part through the seeding of protein aggregates. Ultimately, maintaining proteostasis involves regulating and resolving aberrant protein products that are targeted for clearance by chaperones, the UPS, or autophagy. The key players of these pathways converge at SGs through regulatory mechanisms that are only partly understood.

Many unresolved questions in the field remain. First, how do proteostasis factors regulate SGs differently across stressors and cell types? For example, ZFAND1 mediates VCP and proteasome recruitment to SGs specifically during arsenite stress, suggesting that stress context impacts how SGs are regulated [116,215]. Second, how do different quality control pathways implicated in SG assembly and disassembly intersect and coordinate with each other? For example, VCP couples ubiquitin-dependent protein quality control to both SG assembly and disassembly processes, acting with distinct cofactors and E3 ligases at each stage. Third, do SGs play functional roles in the proteostasis network, and to what extent does this impact disease pathogenesis? For example, the existence of SG-independent TDP-43 and FUS aggregation suggests SGs may not be required for all disease-relevant protein aggregation, underscoring how much remains unresolved about their functional contribution [178,179,195,216]. Thus, future studies that continue to clarify how SGs are regulated, how SGs in turn regulate proteostasis, and the function of SGs as protective or detrimental to cellular health will further our understanding of cellular resilience and disease mechanisms.

Acknowledgments

We thank Moon lab members for their feedback. We apologize for any relevant work not cited due to space limitations.

Author contributions

CRedit: **Rachel Kim:** Writing – original draft, Writing – review & editing, Visualization; **Erika N. Calle Urgiles:** Visualization, Writing – original draft, Writing – review & editing; **Stephanie L. Moon:** Supervision, Visualization, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Generative AI (Claude Opus 4.8 and Gemini) was used for language refinement in editing the manuscript.

Funding

This work was supported by grants to S.L.M. from the NIH/NIGMS [R35GM146711] and from the Robert Packard Center for ALS Research at Johns Hopkins. Its contents are the sole responsibility of the authors and do not necessarily reflect the official views of Johns Hopkins University or any grantor providing funds to the Robert Packard Center for ALS Research. R.K. was supported by the Michigan Medical Scientist Training Program T32 [T32GM156550] and E.N.C.U. by the Career Training in the Biology of Aging T32 [T32AG000114].

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Data availability statement

No new data were created in this study. Data sharing is not applicable to this review article.

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