

# Stress granules: Guardians of cellular health and triggers of disease

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## Abstract

Stress granules are membraneless organelles that serve as a protective cellular response to external stressors by sequestering non-translating messenger RNAs (mRNAs) and regulating protein synthesis. Stress granules formation mechanism is conserved across species, from yeast to mammals, and they play a critical role in minimizing cellular damage during stress. Composed of heterogeneous ribonucleoprotein complexes, stress granules are enriched not only in mRNAs but also in noncoding RNAs and various proteins, including translation initiation factors and RNA-binding proteins. Genetic mutations affecting stress granule assembly and disassembly can lead to abnormal stress granule accumulation, contributing to the progression of several diseases. Recent research indicates that stress granule dynamics are pivotal in determining their physiological and pathological functions, with acute stress granule formation offering protection and chronic stress granule accumulation being detrimental. This review focuses on the multifaceted roles of stress granules under diverse physiological conditions, such as regulation of mRNA transport, mRNA translation, apoptosis, germ cell development, phase separation processes that govern stress granule formation, and their emerging implications in pathophysiological scenarios, such as viral infections, cancer, neurodevelopmental disorders, neurodegeneration, and neuronal trauma.

**Key Words:** apoptosis; axon regeneration; biomolecular condensates; germline cell development; mRNA transport; neurodegeneration; neurodevelopment; pathophysiology; physiological functions; stress granules; translation; viral infection

## Introduction

Since its discovery in 1986, stress granules (SGs) are believed to be a protective response of the cells to various external stressors (Collier and Schlesinger, 1986). SGs minimize cellular damage by storing non-translating pools of messenger RNAs (mRNAs) and limiting the utilization of mRNAs during periods of stress. While cellular stress predominantly inhibits the translation of many mRNAs, it also upregulates the synthesis of specific proteins. The mechanism of SG formation is well conserved across organisms, from yeast to higher mammals. SGs are heterogenous, membraneless organelles containing ribonucleoprotein (RNP) complexes. Although non-translating pools of mRNAs make up the major RNA component of SGs, they are also enriched in noncoding RNAs, proteins such as translation initiation factors, RNA-binding proteins (RBPs), and non-RNA binding proteins. Multiple reports suggest mutations in the genes involved in the assembly or clearance of SGs can lead to abnormal accumulation of SG components (Wheeler et al., 2016), and defects in SG disassembly often lead to aggregating RNPs that play a role in the progression of various human diseases (Table 1). Physiological and pathological functions of SGs are determined by the dynamics of SG assembly and disassembly, with acute SGs being protective against stress and chronic SG being pathological

in nature (Reineke and Neilson, 2019; Jeon and Lee, 2021). Here in this review, we focus on the role of SGs under various physiological and pathophysiological conditions.

During transcription, splicing, and right after synthesis, mRNAs associate with various RBPs to form different types of RNPs (extensively reviewed by Ripin and Parker, 2023). RBPs facilitate mRNA maturation, localization, and temporal expression (Alberti et al., 2017; Tauber et al., 2020). The messenger RNP exits the nucleus through the nuclear pore complex or potentially through a nuclear envelope budding process (De Magistris, 2021; Keuenhof et al., 2023). Once in the cytoplasm, additional protein interactors bind to the RNPs. mRNA and protein interactions are generally modulated by the cis elements in the mRNAs, which are associated with the protein (trans element) (Di Liegro et al., 2014; Fukao et al., 2021; Hopfler and Hegde, 2023). Moreover, post-translational modifications of various RBPs also regulate their affinity for mRNAs. Low-complexity regions in the RBPs generally facilitate interactions between mRNAs and RBPs (Corley et al., 2020; Velázquez-Cruz et al., 2021). When this number of interactions reaches a critical threshold, the RNA and protein complex phase separates from its surroundings and forms an RNP granule through liquid-liquid phase separation and network transition (Millar et al., 2023). Multivalent

interactions between protein-RNA, protein-protein, and RNA-RNA modulate SG formation. SGs show a biphasic structure with a stable core inside and a less concentrated outer shell. The weak intermolecular interactions in the outer shell make dynamic exchanges possible between SGs and cytosol (Wheeler et al., 2016).

While SGs were believed to be temporary storage means for the non-translating pools of mRNAs in the cells undergoing stress, recent advances are unraveling the role of SGs in pathophysiological conditions, such as in axon regeneration and organelle repair (Kedersha et al., 1999, 2000; Sahoo et al., 2018; Andrusiak et al., 2019; Bussi et al., 2023). Additionally, a recent report shows selective mRNA translation inside SGs (Mateju et al., 2020), which challenges the conventional functions of SGs and provides new insight into understanding the role of SGs in cellular homeostasis.

## Search Strategy

The literature cited in this review was obtained by searching the PubMed database and was limited to articles published in peer-reviewed journals from January 2018 until December 2024. Search terms included stress granule + assembly, translation, viral infection, immunity, development, cell survival, neurodevelopment, neurodegeneration,

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**Table 1 | List of diseases associated with stress granule RNA-binding proteins (RBPs)**

Disease(s)/Disorder(s)	Associated RBP(s)	References
Intellectual disabilities and neurodevelopmental disorders- autism spectrum disorders, schizophrenia, fragile X syndrome	EIF4E, FMR1, UPF3B, EIF2S3, CAPRIN1, G3BP1, G3BP2, UBAP2L, AGO2, CYFIP2, EIF4A3, QKI	Aberg et al., 2006; Neves-Pereira et al., 2009; Nguyen et al., 2012; Abekhouk and Bardoni, 2014; Favaro et al., 2014; Mao et al., 2016; Skopkova et al., 2017; Mila et al., 2018; Lessel et al., 2020; Jia et al., 2022
Neurodegenerative disorders - amyotrophic lateral sclerosis, frontotemporal dementia, Parkinson's disease, spinocerebellar ataxia type 2	TDP-43, MATR3, FUS, TAF15, TARDBP, HNRNPA1, ANG, EIF4G1, EIF5A, SFPQ, HNRNPA2B1, UPF1, ATXN2	Van Deerlin et al., 2008; Borroni et al., 2009; Geser et al., 2009; Millicamps et al., 2010; Chartier-Harlin et al., 2011; Ticozzi et al., 2011; van Es et al., 2011; Deng et al., 2014; Scotter et al., 2015; Martinez et al., 2016; Kapeli et al., 2017; Lim et al., 2020; Staszewski et al., 2023; Wator et al., 2023; Tetter et al., 2024
Cancer	TIA1, NPM1, BRF1, GRB7, KHSRP, MEX3A, MSI1, RBM3, RBM42, YBX1, PABPC1, CPEB1, YTHDF2, ZFP36, MAP1LC3A, YTHDF1, DDX6, DCP1A, HNRNPAB, PRMT1, PTBP1, RBM4, NCL, LIN28A, IGF2BP1, AHS1, ZBP1, PUM2, RBPMS, RPS6, FUBP1, KHDRBS1, APOBEC3G, DDX3X, EIF3E, AKAP9, IGF2BP3, EIF5A2	Khalaleh et al., 2013; Wang et al., 2015; Lin et al., 2017; Bielli et al., 2018; Balak et al., 2019; Becker et al., 2019; Glass et al., 2021; Price et al., 2021; Smialek et al., 2021; Yap et al., 2021; Gu et al., 2022; Rabelo-Fernandez et al., 2022; Karki and Kanneganti, 2023; Fan et al., 2024; Zhang et al., 2024
Myotonic dystrophy type 2	CELF1, CNBP	Sun et al., 2011; Peng et al., 2015
Aicardi-Goutières syndrome, dyschromatosis symmetrica hereditaria	ADAR	Rice et al., 2012
Dystonia	PRKRA	Zech et al., 2014
Familial essential thrombocythemia, myelofibrosis, myeloproliferative diseases	CALR	Rotunno et al., 2014; Rumi et al., 2014
Hailey-Hailey disease	ATP2C1	Hu et al., 2000
Male infertility	DAZAP2	Sabetian and Shamsir, 2016
Viral infections (e.g., HIV-1 resistance)	ZC3HAV1	Huang et al., 2010; Zhang et al., 2020

and neural repair. For SG molecular interactome, keywords used were stress granules isolation, stress granule pulldown, and stress granule mass spectrometry. For SG and disease association, the keywords used were stress granule gene mutations + diseases.

## Formation of Stress Granules

SG formation involves complex interactions between proteins and RNAs, as described in **Figure 1**, and they play significant roles in modulating stress responses and maintaining cellular functions.

### Role of RNA-binding proteins in stress granule formation

RBPs play a central role in coordinating cellular responses to stress, including the formation of SGs. Certain RBPs, such as T-cell intracellular antigen 1 (TIA1), Ras GTPase-activating protein-binding protein 1 and 2 (G3BP1 and G3BP2), and Ataxin-2 (ATXN2), exhibit prion-like domains that facilitate self-assembly via oligomerization, serving as nucleation sites for SG formation (Harrison and Shorter, 2017; Wolozin and Ivanov, 2019; Campos-Melo et al., 2021). These RBPs interact with specific mRNAs, promoting their recruitment to SGs and facilitating phase separation (Duan et al., 2019; Yan et al., 2022).

RBPs contain RNA-binding domains that recognize and bind to specific RNA sequences or structural motifs (Yan et al., 2022). These domains include RNA recognition motifs, K-homology domains, double-stranded RNA-binding domains, or other specialized RNA binding domains such as low

complexity domains, and intrinsically disordered regions (IDRs) (Yan et al., 2022). RBPs may contain multiple RNA-binding domains, allowing them to interact with several RNA molecules, enhancing the ability of RBPs to crosslink and nucleate the assembly of SGs. IDRs lack a defined tertiary structure, and RBPs containing multiple IDRs facilitate the formation of liquid-liquid phase separation condensates, such as SGs (Borchers et al., 2021). IDRs may also facilitate multivalent interactions, provide binding sites for other domains, interact with RNA, and stabilize granules, thereby promoting SG formation (Weng and Wang, 2020). IDRs play a vital role in stress-induced cellular compartmentalization, especially under heat stress (Zhu et al., 2020).

TIA1, G3BP1, G3BP2, and ATXN2 are key RBPs involved in SG formation. TIA1 contains a prion-like domain that aids its self-assembly, serving as nucleation sites for SG formation (Wolozin and Ivanov, 2019).

G3BP1 and G3BP2 have three IDRs, which facilitate interaction with mRNAs, leading to their sequestration in SGs. It has been shown that various post-translational modifications of G3BP1, such as phosphorylation, methylation, acetylation, and ubiquitination, repress SG assembly in a context-dependent manner (Tsai et al., 2016; Gal et al., 2019; Sahoo et al., 2020; Gwon et al., 2021). ATXN2, upon phosphorylation, undergoes dynamic changes in its RNA-binding affinity and ability to promote phase separation, influencing SG dynamics (Kaehler et al., 2012). Overall, RBPs play multifaceted roles in mRNA metabolism. They are involved in pre-mRNA splicing, facilitate

mRNA export from the nucleus, regulate mRNA translation, guide mRNAs to specific subcellular locations, and modulate mRNA stability and degradation (Boo and Kim, 2020; Das et al., 2021; Kretova et al., 2023). RBPs interact with mRNA molecules to form complexes, which serve as platforms for protein-protein interactions that are crucial for various cellular processes (Rissland, 2017). Aberrant mutations in RBPs involved in SG assembly can disturb SG homeostasis (**Figure 1**) and eventually lead to various kinds of disorders, as listed in **Table 1**. This suggests that although SGs have always been studied under stress conditions, these granules potentially play roles during physiological environments.

### Role of mRNAs in stress granules formation

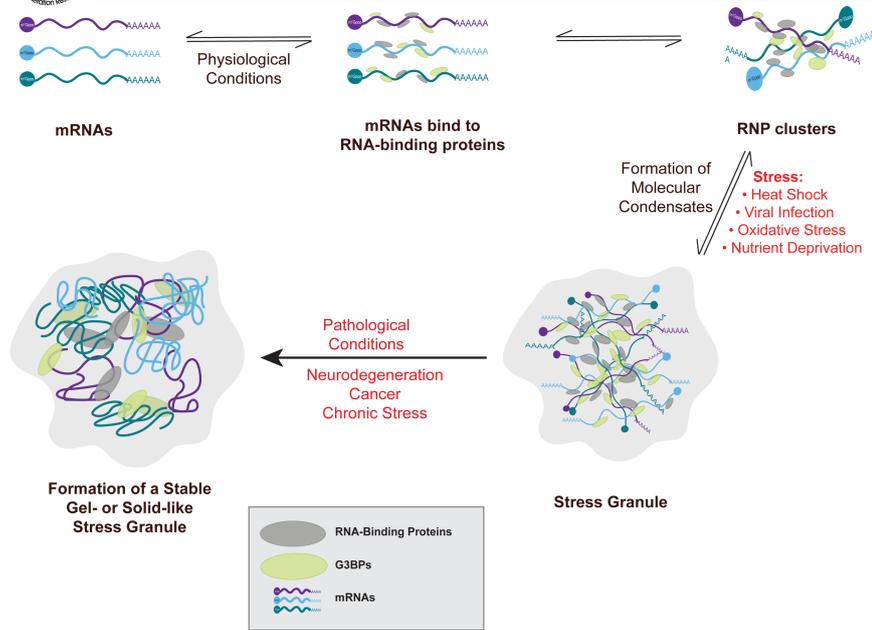
mRNAs, the molecules responsible for carrying genetic information from DNA to protein synthesis, undergo a complex journey within the cell. Following processing, mature mRNA molecules contain protein-coding sequences CDS, as well as untranslated regions UTRs at the 5' and 3' ends, which regulate the spatiotemporal expression of the mRNA. mRNAs serve as scaffolds for the assembly of RBPs within SGs, providing binding sites for protein-protein interactions (Cid-Samper et al., 2018; Campos-Melo et al., 2021; Matheny et al., 2021), and the presence of mRNAs within SGs facilitates the assembly of RBPs into higher-order complexes, lowering the threshold for liquid-liquid phase separation and promoting SG formation (Roden and Gladfelter, 2021). mRNA molecules enhance RBP phase separation and influence the dynamic assembly and disassembly of SGs (Maharana et al., 2018).

Length of mRNAs has been shown to be positively correlated with SG assembly as longer mRNAs have more sites for intermolecular RNA-RNA and RNA-protein interactions (Ries et al., 2023). Recent findings show that N6-methyladenosine (m<sup>6</sup>A) modifications in mRNAs modulate SG targeting (Khong et al., 2022). m<sup>6</sup>A modifications have also been shown to prevent the targeting of RNAs to SGs by altering RNA structure and protein interactions (Arguello et al., 2017; Edupuganti et al., 2017; Khong et al., 2022). m<sup>6</sup>A modifications destabilize certain RNA duplexes, making specific binding sites inaccessible to proteins involved in SG formation (Hofler and Duss, 2024). Additionally, m<sup>6</sup>A can disrupt the assembly of protein-RNA complexes necessary for SG recruitment, thereby reducing the ability of modified RNAs to localize to SGs (Hofler and Duss, 2024). Poly-adenylated mRNAs are known to be enriched in SGs. The preference for poly-adenylated mRNAs in SG formation is attributed to the role of poly-A tails in mRNA stability and translation (Passmore and Collier, 2022).

Overall, mRNAs are one of the major components of SG and facilitate SG assembly by lowering the threshold for phase separation.

## Molecular Components and Associated Pathways of Stress Granules

SGs are generally considered to be uniform with respect to their molecular composition. So, we wanted to confirm this by comparing



**Figure 1 | Formation of stress granules under physiological and pathophysiological conditions.**

mRNAs associate with RNA-binding proteins, including G3BP1 and G3BP2, to form ribonucleoprotein clusters, which are membrane-less organelles. These clusters phase separate and aggregate into molecular condensates called stress granules (SGs) that exhibit a dynamic liquid-like behavior. Under physiological conditions, SGs exchange molecules with their environment and maintain SG homeostasis. Under stress, these SGs assemble and inhibit translation, and this process is reversed when the stressor is removed. However, under pathological conditions such as neurodegeneration, cancer, and chronic stress, these clusters aggregate into gel- or solid-like SGs, resulting in dysregulated SG homeostasis.

different studies to identify the common protein and mRNA components of SGs and the common associated pathways. To analyze the SG components, SGs are isolated from cell lysates using differential centrifugation followed by sucrose gradient fractionation or by employing various other biochemical methods, such as immunoprecipitation using antibodies against core SG proteins (e.g., TIA-1, G3BP1) (Wheeler et al., 2017; Kosmacz et al., 2019; Youn et al., 2019).

Once isolated, the RNA content of SGs is analyzed using high-throughput sequencing techniques, such as RNA sequencing. RNA sequencing allows for the comprehensive profiling of mRNAs present within SGs, providing insights into the transcriptomic landscape under stress conditions (Khong et al., 2018). Bioinformatics analysis of RNA sequencing data enables the identification of specific mRNAs enriched in SGs compared with the total cellular transcriptome. These mRNAs encompass a wide range of functional categories, including cell cycle regulators, tumor suppressors, apoptosis regulators, and structural proteins (Campos-Melo et al., 2021; Fefilova et al., 2022). The sequestration of specific mRNAs within SGs serves as a mechanism for the rapid modulation of gene expression in response to cellular stress. Under stress conditions, most of the mRNAs are translationally suppressed and are recruited to SGs for storage, allowing cells to prioritize the translation of stress-responsive mRNAs. The RNA content of SGs reflects the cellular state and the nature of the stress stimulus, with the specific mRNAs present in SGs depending on the cell type and the stressor encountered. By sequestering and regulating the translation of specific mRNAs, SGs enable cells to adapt to stressful conditions and maintain cellular homeostasis.

Similarly, proteomic analysis of isolated or immunoprecipitated SGs by mass spectrometry shows that SGs are enriched with a diverse array of RBPs that play crucial roles in the regulation of mRNA metabolism and translation. Among these RBPs, G3BP1 and G3BP2 emerge as key scaffold proteins in SGs, which interact with both RNA and other RBPs, orchestrating the assembly and disassembly of SGs (Yang et al., 2020). Through techniques such as G3BP1 RNA immunoprecipitation combined with RNA sequencing, studies have identified the G3BP1-associated mRNAs as a proxy for SG-residing mRNAs (Somasekharan et al., 2020; Seo and Kleiner, 2023).

Additionally, TIA-1 and TIA-R have been identified as key regulators of SG assembly and disassembly (Peng et al., 2022). These RBPs bind to specific mRNAs, including those encoding stress proteins such as Bcl-2 and Cyclin D1 (Kedersha and Anderson, 2007). Caprin-1, another RBP found in SGs, plays a crucial role in the regulation of mRNA translation. Through its interaction with translation initiation factors and other RBPs, Caprin-1 modulates the translational status of mRNAs within SGs (Song et al., 2022). Together, the protein components of SGs include heat shock proteins, chaperones, and components of the translational machinery, which regulate RNA metabolism, translation regulation, and stress response pathways, highlighting the dynamic nature of SGs.

#### Analytical comparisons of the studies

As discussed in the previous section, the mRNAs and protein components of SGs vary and depend on the kind of stressor used in the study. So, in this review, we have compared different studies, which

isolated SG-associated mRNAs and proteins either under stress or no-stress conditions.

For SG mRNA contents, we compared four studies reporting mRNAs associated with SG in stressed or non-stressed conditions (Table 2). We performed DeepVenn analysis of these data sets to identify common mRNAs, which associate with SGs in stress conditions (Hulsen, 2022; Figure 2A and Additional Table 1). Our analysis shows that the SG-associated mRNAs reported in the Namkoong et al. (2018)'s study segregate as separate entities and do not show any overlap with the other three studies. In this study, the authors applied two different stressors (sodium arsenite and endoplasmic reticulum stress) to HEK293 cells and isolated SGs by differential centrifugation. The other three studies make a separate cluster but, once again, do not show a large overlap (Khong et al., 2017; Matheny et al., 2019; Somasekharan et al., 2020). Matheny et al. (2019) subjected U2OS cells to sodium arsenite stress and isolated SGs by differential centrifugation. Khong et al. (2017) isolated the SG-associated mRNAs from U2OS cells by immunoprecipitating G3BP1 after sodium arsenite stress. Somasekharan et al. (2020) performed proximity biotinylation in G3BP1-APEX expressing U2OS cells to identify SG-associated mRNAs. From our analysis, the lack of common SG-associated mRNAs between different studies shows that the targeting of mRNAs to SGs is dependent on the cell type, the kind of stress, and the method used to isolate the SGs.

We further compared the SG-associated mRNAs from two studies under no-stress conditions (Matheny et al., 2019; Somasekharan et al., 2020; Figure 2B and Additional Table 2). Results from our analysis show that there is a strong overlap between SG-associated mRNAs in stress vs. no-stress conditions in Matheny et al. (2019) datasets. The same analysis for the Somasekharan et al. (2020) datasets showed some degree of overlap but not to the extent of Matheny et al. (2019) (Figure 2B). Moreover, when we compared the SG-associated mRNAs in no-stress conditions from both studies, it resulted in very few common mRNAs (Figure 2C and Additional Table 3). While Matheny et al. (2019) used differential centrifugation to isolate the SGs, which favors SG core isolation, Somasekharan et al. (2020) used proximity biotinylation, which possibly favors biotinylation of peripheral SG components. Our results show that the SG core-associated mRNAs remain the same to a large extent in both stress and no-stress conditions, which suggests that the core SG components exist even in the absence of stress and most probably are functional under physiological conditions.

For our common protein component analysis, we compared mass spectrometry datasets from three different studies (Jain et al., 2016; Markmiller et al., 2018; Curdy et al., 2023). In these studies, Jain et al. (2016) and Curdy et al. (2023) have used G3BP1 immunoprecipitation, and Markmiller et al. (2018) have used G3BP1-APEX proximity biotinylation with sodium arsenite-treated cells to isolate SGs but in three different cell lines. Our analysis shows that the SG-associated proteins in Markmiller et al. (2018) and Curdy et al. (2023) show higher overlap with the dataset from Jain et al. (2016) (Figure 2D and Additional Table 4),

but there are very few common proteins between these data sets. Although our SG mRNA/protein comparison analyses did not show strong overlaps, molecular pathway analysis of these studies showed some common pathways. For example, RNA transport and spliceosome pathways, regulation of translation, cellular response to stress, and RNA binding are some of the molecular pathways that are common across all these studies. This suggests that although different molecular components are used in SGs in different cells under various stress conditions, their molecular functions are similar. Both mammalian and yeast models, as studied by Khong et al. (2017), exhibit similar molecular pathways in response to stress, pointing to a fundamental cellular strategy across different organisms. Furthermore, the observations in human T lymphocytes by Curdy et al. (2023) and neural progenitor cells by Markmiller et al. (2018) demonstrate that these mechanisms are preserved across various human cell types, reflecting the universal importance of SGs in cellular homeostasis. Our findings suggest that the components of SGs are cell-type and context-specific. So, care should be taken while designing a study to analyze SG components.

### Physiological Functions of Stress Granules

SGs are essential cellular structures that help cells cope with stressful conditions by temporarily halting protein synthesis and storing mRNAs. Important physiological roles of SGs are discussed in detail in the following section and represented in Figure 3.

#### mRNA triage

SGs sequester non-translating mRNAs and translation initiation components and interact with other RNA granules to modulate mRNA function and stability (Ivanov et al., 2019; Escalante and Gasch, 2021). mRNAs can dynamically move in and out of SGs, indicating a role in transient storage and transport rather than permanent sequestration (Moon and Parker, 2018). Thus, SGs play a pivotal role in mRNA triage by dynamically sorting and stabilizing mRNAs. The formation of SGs involves the release of mRNAs from polysomes and the subsequent clustering of RBPs, which undergo conformational changes to facilitate granule formation (Guillen-Boixet et al., 2020; Yang et al., 2020). Based on the cellular environment, mRNAs present in SGs can have one of the following fates: (1) stored in SG in translationally silent condition, (2) transferred to P-bodies for degradation, (3) transferred back to polysomes for translation.

SG formation is modulated by various post-translational modifications, and ATP-dependent remodeling complexes, maintaining their dynamic state, as described in a review by Protter and Parker (2016). Only specific types of mRNAs can accumulate in SGs, with targeting efficiency varying widely among different mRNAs. mRNAs with longer coding and UTR regions and poor translatability are more likely to be sequestered in SGs. Specific motifs, such as AU-rich elements, are associated with mRNA sequestration in SGs during stress (Namkoong et al., 2018). Most mRNAs sequestered in SGs recover nearly completely

Table 2 | Reports analyzed for stress granule (SG) content analysis (details in Figure 2)

	Sr.No.	References	Assay to isolate RNA	Cell line	Type of stress
mRNA studies	I.	Khong et al., 2017	G3BP1 immunoprecipitation, RNA-sequencing	U2OS	Sodium arsenite
	II.	Matheny et al., 2019	SG isolation, RNA-sequencing analysis	U2OS	Sodium arsenite
	III.	Somasekharan et al., 2020	APEX tagged G3BP1 overexpression, RNA-sequencing	PC-3	Sodium arsenite
	IV.	Namkoong et al., 2018	Extracted RNA from cytosolic and ribonucleoprotein granule fractions after stress treatments, RNA-sequencing	HEK293	Sodium arsenite, endoplasmic reticulum stress
Protein studies	I.	Curdy et al., 2023	Anti-G3BP1 antibody immunoprecipitation, Mass Spec	CD3' T	Sodium arsenite
	II.	Jain et al., 2016	Anti-G3BP1 antibody immunoprecipitation, Mass Spec	U2OS	Sodium arsenite
	III.	Markmiller et al., 2018	APEX-G3BP1, proximity biotinylation, Mass Spec	HEK293	Sodium arsenite

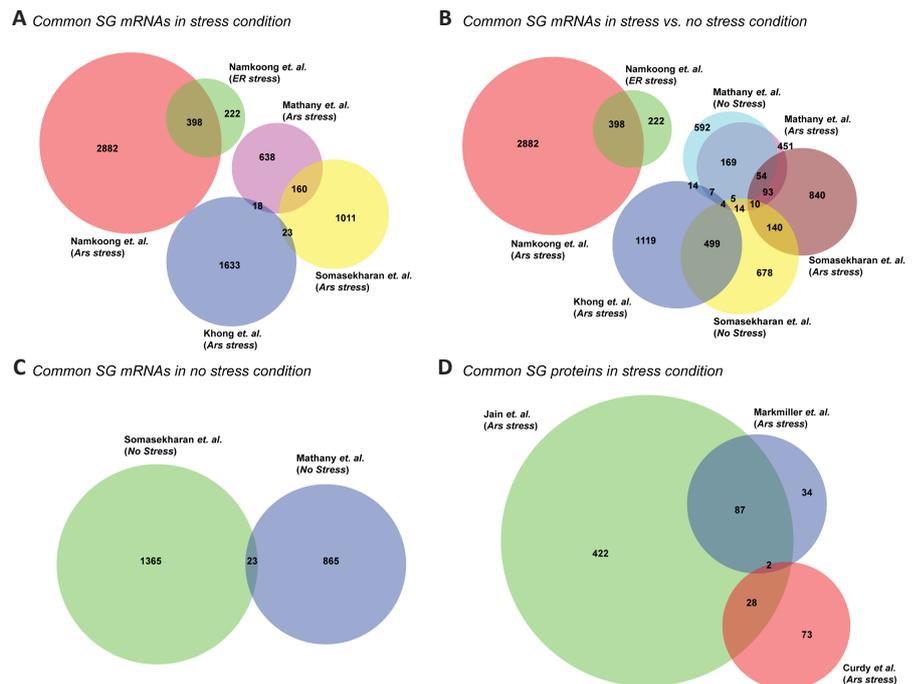


Figure 2 | Comparison of stress granule (SG) mRNA and protein components from various studies as in Table 2. (A–C) Venn diagrams show comparative analysis of different studies reporting SG-associated mRNA in stress conditions (A), in stress and no stress conditions (B), and in non-stress conditions (C). (D) Venn diagram shows a comparative analysis of different studies reporting SG-associated proteins in stress conditions.

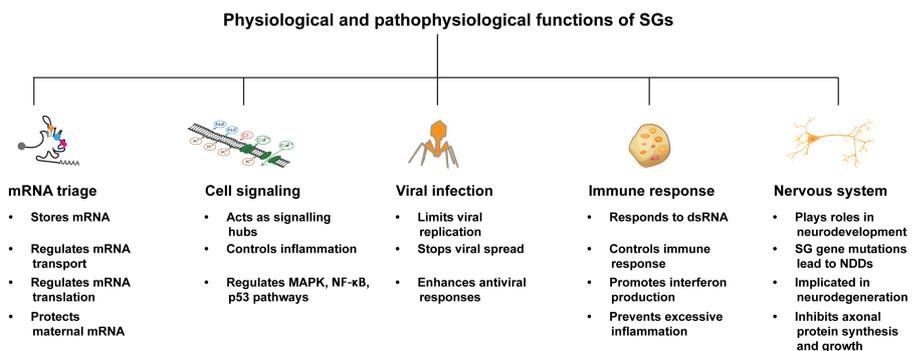


Figure 3 | Physiological and pathophysiological functions of stress granules (SGs). The illustration shows the various functions SGs play under physiological and pathophysiological conditions. SGs play a critical role in various biological processes, particularly in the regulation of mRNA translation. In germline cells, SGs protect maternal mRNA and maintain germline function through the formation of specific ribonucleoprotein (RNP) granules. SGs function as signaling hubs, impacting key pathways such as mitogen-activated protein kinase (MAPK), nuclear factor (NF)-κB, and p53, thereby regulating inflammation. SGs are also essential for viral defense, as they limit viral spread by responding to viral double-stranded RNA (dsRNA) and enhancing antiviral sensors that bolster immune responses. Recent pieces of evidence show that SGs regulate neuronal development, and defects in SG formation or clearance can lead to neurodevelopmental disorders (NDDs), neurodegeneration, and defective neural repair.

for translation after removal of stress, with m<sup>6</sup>A-modified mRNAs showing a higher recovery rate compared with unmodified mRNAs (Das et al., 2021). Therefore, SGs are not static storage sites for mRNAs but dynamic hubs where mRNAs can shuttle between SGs and the cytoplasm.

#### mRNA translation

While the formation of SGs is facilitated by global translational suppression, it is debated if SGs also suppress translation. Various reports show that SGs may enable selective translation by promoting the translation of transcripts not targeted to SGs. Notably, stress-induced transcripts, which are often translated despite global translational shutdown, may escape condensation. For example, highly translated stress transcripts such as *Hsp70* and *Hsp90* do not associate with SGs under stress and are actively translated (Glauninger et al., 2022). Despite this, SGs are believed not to be essential for global translational shutdown, as translation likely occurs alongside a more dominant inhibitory mechanism (Escalante and Gasch, 2021). Moreover, observations of translation occurring within SGs further suggest that SGs restructure the translome rather than suppressing global translation (Mateju et al., 2020). A recent study showed that G3BP1 and G3BP2 act in a non-redundant manner to anchor the tuberous sclerosis complex to lysosomes and suppress activation of the mTORC1 by amino acids and insulin (Prentzell et al., 2021). In this study, the authors also show that inhibition of G3BPs activates the mTOR signaling.

In peripheral nervous systems (PNS) axons, G3BP1 forms SG-like structures under physiological conditions and associates with specific axonal mRNAs such as *Nrn1* and *Kpnb1* (Sahoo et al., 2018). Over-expression of G3BP1 is known to induce SG formation (Kedersha et al., 2005; Reineke et al., 2012, 2015; Matsuki et al., 2013; Takahashi et al., 2013), and G3BP1 overexpression in dorsal root ganglion neurons inhibits axonal translation of *Nrn1* and *Kpnb1*. Moreover, inhibiting the functions of G3BP1 in PNS or central nervous system axons increases global axonal protein synthesis (Sahoo et al., 2018). Overall, it suggests that axonal SGs can inhibit the translation of specific mRNAs that they associate with and restructure the cellular translome by allowing or inhibiting the translation of specific mRNAs.

#### mRNA co-transport

SGs can act as platforms for the assembly and transport of various cellular components. Proteins and RNA molecules can associate with SGs, forming a complex (Van Treeck et al., 2018). SG, with its associated cargo, can be transported along cellular tracks, such as microtubules or actin filaments. Actin and microtubules play complementary roles. Lamellar actin confines SGs, and its retrograde flow drives them toward the cell center. Microtubules, in turn, adhere to SGs through capillary interactions, which tend to concentrate SGs in microtubule-rich regions near the nucleus (Böddeker et al., 2023). Motor proteins often mediate this transport. Upon reaching their destination, the SG can disassemble, releasing its cargo. This process, often referred to as “piggybacking,” allows for the efficient movement of these components within the cell.

Long-distance RNA transport enables local protein synthesis at metabolically active sites distant from the nucleus. This process ensures an appropriate spatial organization of proteins vital to polarized cells such as neurons. This is a mechanism for RNA transport in which RNA granules hitchhike on moving lysosomes. Annexin A11, an RNA granule-associated phosphoinositide-binding protein, acts as a molecular tether between RNA granules and lysosomes (Liao et al., 2019). Overall, specific RBPs, mRNAs, or other molecules can hitch a ride with SGs to facilitate their transport, localization, or sequestration during cellular stress, leveraging the SGs’ dynamic assembly and disassembly properties.

#### Germline cell development

Different from the soma, germ lines have pluripotency. Like SGs, germline cells have RNP granules called germ granules, which contain proteins and RNAs that are required specifically for germ cell development. Germ granules are involved in regulating fertility by acting as hubs for RNA metabolism and posttranscriptional gene expression control, which is a key part of germ cell differentiation (Reineke and Neilson, 2019; Trcek et al., 2020). Germline cells also respond to stressors by assembling RNP granules, which are similar to SGs.

Oocytes, or immature egg cells, store large amounts of maternal mRNA to support early embryonic development post-fertilization (Winata et al., 2018). Oocytes, being in extended meiotic arrest, store maternal mRNAs in such RNP granules for a longer duration before fertilization. Germ granules regulate maternal mRNAs post-transcriptionally and are crucial for maintaining embryonic viability (Flora et al., 2018; Parker et al., 2020; Scholl et al., 2024). RNP granules in germ cells are adaptive and regulate gene expression by protecting maternal mRNAs from degradation or early translation during extended meiotic arrest (Wood et al., 2016). TIAR-1 (the mammalian homolog of TIA1), protects the *Caenorhabditis elegans* (*C. elegans*) germline from heat shock, preserving mRNAs for proper development (Huelgas-Morales et al., 2016). In the embryo and oocyte of *C. elegans*, the formation of PQN-59 cytoplasmic granules that colocalize with GTBP-1 (the mammalian homolog of G3BP1), provides protection against heat stress during development (Abbatemarco et al., 2021). Collectively, these findings indicate that SGs in germline cells, involving unique components and mechanisms, are crucial for the integrity and function of germline cells during stress and normal physiological functions.

#### Cellular signaling

The strategic sequestration of mRNAs within SGs can prevent or delay the translation of key signaling mRNAs. Thus, SGs act as a switchboard for signal propagation within cells. Interactions between SGs and various signaling cascades underscore a complex communication network that dictates cell survival or apoptosis. In addition to protecting mRNA integrity under stressful conditions, SGs also play ambiguous roles by potentially propagating signals that lead to pathological conditions such as cancer or neurodegeneration (Advani and Ivanov, 2020; Marcelo et al., 2021; Zhou et al., 2023). SGs

act as RNA-centric signaling hubs, sequestering signaling proteins and altering multiple signaling pathways, which may be facilitated by IDRs in RNA-binding and signaling proteins (Mahboubi and Stochaj, 2017). SGs interact with the NLRP3 inflammasome with the SG protein DDX3X playing a role in regulating inflammasome activation (Samir et al., 2019). The kinase DYRK3 regulates the condensation and dissolution of SGs, linking SG dynamics to mTORC1 signaling, which is crucial for cell growth and proliferation (Rehbein et al., 2021). SGs may also rewire signaling events to maintain homeostasis and have been implicated in the negative regulation of MAPK signaling by sequestering signaling components such as PKC/Pck2 (Sugiura, 2021). The strategic sequestration of mRNAs within SGs can prevent or delay the translation of downstream key signaling molecules like those mediated by nuclear factor- $\kappa$ B and p53, and act as a switchboard for signal propagation within cells (Haronikova et al., 2019; Paget et al., 2023). Taken together, SGs regulate cellular signaling pathways by sequestering key signaling molecules, such as kinases, phosphatases, and mRNAs, thereby modulating their availability and activity to fine-tune stress responses, protein synthesis, and cell survival mechanisms.

#### Cell survival

SGs are crucial modulators of cell fate, often tipping the balance towards survival rather than apoptosis. SGs promote cell survival by enhancing pro-survival activity, minimizing stress-related damage, inhibiting apoptosis, and aiding in stress recovery. Several reports indicate that many SG proteins are important for cell survival. G3BP1 and Gle1A show cell protective function by enhancing survival responses (Glass and Wente, 2019; Lo et al., 2020). TIA1, when oxidized, leads to impaired SG formation and signals for apoptotic death, whereas expressing TIA1 mutant, which cannot be oxidized, rescues SG formation and impairs apoptosis (Arimoto-Matsuzaki et al., 2016). Kinases within SGs also play an essential role in SG assembly and cell survival. For example, S6 kinases (S6K1 and S6K2) are involved in SG assembly and maintenance, and they promote cell survival under oxidative stress by regulating mTOR signaling (Sfakianos et al., 2018).

Cellular apoptosis is triggered by various stress-responsive pathways, and the formation of SGs enhances cell survival by inhibiting pro-apoptotic signals. SGs have a direct role in suppressing various stress-responsive pathways such as SAPK, P53-mediated, and caspase-mediated pathways. SG formation negatively regulates the stress-activated p38 and JNK MAPK (SAPK) pathways, which are involved in apoptosis (Sugiura, 2021). SGs sequester activated RhoA and ROCK1, preventing ROCK1 from interacting with JNK-interacting protein 3 and activating the JNK pathway, thereby protecting cells from apoptosis (Tsai and Wei, 2010). The availability of mRNAs for stress-responsive genes can be controlled by restraining their negative regulators within SGs, as reported with the entrapment of hCdc73 to regulate mRNA stability of the p53, which is a central regulator of apoptosis (Lee et al., 2023). SGs also stabilize anti-apoptotic factors, thus inhibiting apoptosis. SGs stabilize the mRNA of anti-apoptotic proteins such as p21WAF1/CIP1

through the action of SG-associated proteins such as CUGBP1, which has been shown to prevent bortezomib-mediated apoptosis (Fournier et al., 2024). The mTORC1-eIF4E pathway promotes SG formation, which, in turn, stabilizes anti-apoptotic pathways, including the p21 pathway. Inhibition of this pathway disrupts SG formation and sensitizes cells to apoptosis (Fournier et al., 2024).

SGs play a significant role in inhibiting reactive oxygen species production and preventing reactive oxygen species-dependent apoptosis, primarily through the actions of specific proteins such as G3BP1 and USP10 (Dong et al., 2019; Takahashi et al., 2022). G3BP1 overexpression reduces reactive oxygen species levels and provides cytoprotection against oxidative stress and related cellular damage (Dong et al., 2019). Additionally, the ubiquitination of SG proteins plays a very important role in the recovery of cellular activities. For example, ubiquitinated G3BP1 forms a complex with VCP and FAF2, which is necessary for SG disassembly during recovery (Gwon et al., 2021). Collectively, these findings indicate that SGs enhance cell survival by inhibiting apoptosis through various mechanisms. These insights underscore the protective role of SGs in cellular stress responses and their potential implications in disease contexts.

## Pathophysiological Functions of Stress Granules

### Virulence and viral resistance

Host cells induce SG formation upon viral infection as a physiological defense to inhibit viral replication by sequestering viral mRNAs (Eiermann et al., 2020). SGs contribute to antiviral defense by coordinating antiviral signaling cascades and the integrated stress response (Eiermann et al., 2020). Viruses also target SGs to be manipulated by viral factors to promote their replication by interfering with the formation and function of SGs (Sadasivan et al., 2022). Viruses such as poliovirus, Mammalian Orthoreovirus, Influenza virus, HTLV-1, West Nile virus, HCV, and Human Herpes viruses affect SG formation and influence their function (Guo et al., 2018; Guan et al., 2023). SGs are targeted by viruses to overcome host cell inhibition, with SARS-CoV-2 as a notable example, where the virus can improve translation by targeting SG to have a proviral effect (Gordon et al., 2020; Luo et al., 2021; Long et al., 2024). The protein G3BP1 is critical for virus-induced SG formation and viral replication, suggesting that viruses may exploit SGs for replication (Wen et al., 2020; Zhao et al., 2022). Porcine epidemic diarrhea virus infection leads to cleavage of G3BP1, and this process is mediated by caspase-8 (Gao et al., 2021). Besides, protease 2A of poliovirus induces the generation of SGs at first, and the cleavage of G3BP1 by PV3C protease leads to SG disassembly later (Yang et al., 2018). Middle East Respiratory Syndrome Coronavirus inhibits SG formation by inhibiting PKR-mediated eIF2 $\alpha$  phosphorylation (Nakagawa et al., 2018).

Virus-induced SGs, termed “antiviral stress granules” (avSGs), act as platforms for antiviral sensors, but viruses such as coronaviruses have strategies to suppress avSG formation to counteract host immune responses (Yoo, 2024).

Together, the interplay between SG formation and viral strategies to disrupt or evade these granules emphasizes the importance of SGs in the host-pathogen conflict.

### Innate immune response

Viral infection often produces double-stranded RNA (dsRNA), a potent immune stimulant, in the host cell. The host cell recognizes dsRNA as a foreign invader and initiates an immune response to eliminate the virus (Li and Wang, 2023). SGs can directly interact with RIG-I-like receptors (RLRs), such as RIG-I and MDA5, which are key sensors of viral dsRNA. Once in the SGs, RLRs may be activated or inhibited, depending on the specific circumstances. G3BP1 acts as a co-sensor and activates RIG-I, and this interaction leads to increased interferon production (Kang et al., 2021), while G3BP suppression leads to hyperactivation of RLR activity and immune-mediated cell death (Paget et al., 2023). Thus, modulation of RLR by SGs protein can significantly impact the magnitude of the immune response, influencing factors such as the production of type I interferons and the activation of downstream signaling pathways. In some cases, SGs may interact with Toll-like receptors (TLRs), particularly those involved in recognizing viral nucleic acids, such as TLR3 and TLR7. This interaction could potentially influence TLR signaling, production of inflammatory cytokines, and the activation of innate immune cells (Kawai et al., 2024).

SGs also play a role in regulating immune signaling pathways by sequestering key components of these pathways. SGs can modulate the intensity and duration of the immune response. This helps to ensure that the immune response is appropriate and does not cause excessive damage to the host cell (Mateju et al., 2020). SGs can play a pivotal role in regulating the activity of nuclear factor- $\kappa$ B, a transcription factor that is central to inflammatory responses and influences interferon production by modulating downstream signaling pathways, such as the JAK-STAT pathway (Li et al., 2023; Samir and Tarek, 2023). SGs can help to dampen excessive inflammation by preventing the release of excessive inflammatory mediators (Paget et al., 2023). SGs may also play a role in preventing autoimmune diseases by regulating immune responses (Wang et al., 2020). In summary, SGs are rare and specific mechanisms that cells employ to control dsRNA-triggered immune responses. By acting as shock absorbers, SGs help to prevent excessive inflammation and autoimmune reactions, ensuring that the immune response is appropriate and effective. Further research is needed to fully understand the complex roles of SGs in immune regulation and to explore their potential as therapeutic targets for immune-related diseases.

### Cancer

Interestingly, SGs play a dual role in cancer. They can contribute to tumor progression, metastasis, and resistance to therapy and can promote cell survival. SGs are involved in tumorigenesis and metastasis through tumor-associated signaling pathways (Gao et al., 2019; Legrand et al., 2020; Lee and Namkoong, 2022; Wang et al., 2022). Disrupting SG formation or function has been

shown to inhibit tumor progression and sensitize cancer cells to chemotherapy (Gao et al., 2019; Park et al., 2020; Hu et al., 2022; Wang et al., 2022). Targeting SGs or their components offers a promising avenue for cancer treatment, potentially improving the efficacy of existing therapies and overcoming chemoresistance. Specific SG proteins, such as G3BP1, TIA1, and YB1, have been identified as potential targets for therapeutic intervention (Park et al., 2020; Asadi et al., 2021; Hu et al., 2022). The expression levels of SG proteins may also serve as valuable prognostic markers, aiding in the personalization of cancer treatment strategies (Aulas et al., 2015). We are not discussing all the functions in detail here as these topics have already been covered by some excellent literature reviews in the past (Lavalee et al., 2021; Zhou et al., 2023; Jia et al., 2024).

### Neuronal pathophysiology

SGs are implicated in neurodevelopment and neurodevelopmental disorders. A recent report has directly linked SG proteins to autism spectrum disorders (Jia et al., 2022). The authors found significant enrichment in 31 SG genes. Some of these are previously known and some are newly identified neurodevelopmental disorder genes, including the core SG genes, *G3BP1*, *G3BP2*, and *UBAP2L* (Jia et al., 2022). Out of these genes, *G3BP1* is the most studied one for its role in SG assembly and neurodevelopment. Loss of *G3BP1* is embryonically lethal in 129/Sv mice (Zekri et al., 2005), but with a Balb/c background, the *G3BP1*<sup>-/-</sup> mice show altered synaptic plasticity and Ca<sup>2+</sup> homeostasis (Martin et al., 2013). *G3BP1* granules are also important for dendritic spine maturation (Lo et al., 2020). Interestingly, several of the neurodevelopmental disorder-linked mutations in *G3BP1/2* genes fail to assemble SGs in HeLa cells (Jia et al., 2022).

SGs play a dual role in neurodegenerative diseases. They are essential for cellular stress responses but can also contribute to disease pathology when dysregulated. Persistent SGs, often due to chronic stress or genetic mutations, can promote the aggregation of pathological proteins, exacerbating diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia, and Alzheimer’s disease. RNA-binding proteins are central to SG function and frequently implicated in neurodegenerative diseases, as Asadi et al. (2021) reviewed in detail. In contrast, SGs help mitigate neurodegenerative cascades by transiently storing mRNAs and allowing selective translation of stress-response proteins, which can be protective in conditions such as ALS and frontotemporal dementia (Glineburg et al., 2024). SGs prevent the aggregation of phosphorylated TDP-43, a hallmark of ALS, under short-term stress, thereby reducing neurodegeneration (Prasad et al., 2019; Streit et al., 2022). Inhibiting *G3BP1* function has been shown to disassemble mutant TDP43 aggregates and rescue defective neuromuscular junctions caused by aberrant SGs in ALS models (Altman et al., 2021). Contrary to these findings, overexpression of *G3BP1* has been shown to reduce pathological poly-Q aggregation (Gutiérrez-García et al., 2023).

Stress granules are increasingly recognized for their critical role in axonal regeneration post-injury by modulating the translation of proteins essential for axonal repair and growth. SGs may function as dynamic molecular hubs, regulating the on-demand local protein synthesis required for successful axon regeneration. G3BP1 has been shown to localize to mammalian PNS axons, form molecular condensates under physiological conditions, interact with specific axonal mRNAs, and inhibit axonal protein synthesis (Sahoo et al., 2018). Further, these axonal SGs have also been shown to be present in central nervous system axons (Sahoo et al., 2024). In PNS neurons, an intrinsic molecular mechanism regulates the axonal SGs, where axonal injury induces local translation of the casein kinase 2 alpha (*Csnk2a1*) mRNA to synthesize CK2a protein, which phosphorylates G3BP1 to disassemble the axonal SGs to promote axon regeneration (Sahoo et al., 2020). Similarly, in *C. elegans*, axonal granules of the orthologue of TIA1 attenuate axon growth (Andrusiak et al., 2019). Overall, these reports suggest that SG homeostasis is important for proper neuronal function, and aberrations in this process can lead to neurodevelopmental defects, neurodegeneration, and impaired neural repair.

## Conclusion and Future Perspective

Under cellular stress, SGs change the translationalome of cells by sequestering the non-translating mRNAs and preventing their degradation. This process also helps the cells to focus energy on synthesizing stress-responsive proteins required for cellular survival. The mRNA and protein composition of SGs are highly context-dependent, as we have covered in detail in our review. It varies greatly depending on the kind of cell, the type of stressor, and the experimental methods employed to examine them. Different cell types prioritize distinct sets of mRNAs and proteins in SGs based on their physiological roles, while stressors such as sodium arsenite, endoplasmic reticulum stress, or viral infection trigger unique SG components suited to mitigating specific types of damage. Moreover, additional heterogeneity is introduced by the SG detection techniques, such as cell fractionation, proximity biotinylation, immunoprecipitation, or high-resolution imaging, which may affect the identification of specific SG components. This variation in SG composition reveals the intricacy of SG formation and function, implying that SGs can serve tailored functions in a context-dependent manner. In general, it is still challenging to define a “universal” SG composition; current understanding emphasizes the need for more focused, context-driven research into SG biology.

Future research should use standardized methods for the analysis of SG mRNA and protein components across different cell types and stress conditions to facilitate comparison across studies. This will provide light on the diverse functions SGs may play in various physiological and pathological circumstances by identifying common SG components as well as cell- or stress-specific variations. Furthermore, investigating how signaling pathways, post-transcriptional, and post-translational changes control the inclusion of particular mRNAs and proteins in SGs

would enhance our comprehension of how SG composition is regulated. Comprehending these differences could also offer an understanding of why particular cell types are more vulnerable to SG-related disorders and could result in cell-type- or stressor-specific treatment strategies for ailments like cancer and neurodegeneration.

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**Additional files:**

**Additional Table 1:** *Detailed data for Figure 2A.*

**Additional Table 2:** *Detailed data for Figure 2B.*

**Additional Table 3:** *Detailed data for Figure 2C.*

**Additional Table 4:** *Detailed data for Figure 2D.*

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## 应激颗粒：细胞健康的守护者与疾病的触发者

### 文章特色分析

#### 一、文章重要性

##### 1. 系统性综述 SG 的多功能性：

- 文章全面总结了应激颗粒在细胞应激响应、mRNA 代谢、信号转导、发育、免疫、癌症、神经发育与退行性疾病等多个生物学过程中的作用，强调了其在细胞稳态维持与疾病发生中的核心地位。

##### 2. 连接基础研究与临床病理：

- 文章不仅阐述了 SG 的生理功能，还深入探讨了其在神经退行性疾病、癌症、病毒感染、免疫调节等病理过程中的作用，为理解多种疾病的分子机制提供了新视角。

##### 3. 强调 SG 动态性的双重角色：

- 明确提出急性 SG 形成具有保护作用，而慢性 SG 积累则具有病理性质，这一观点对理解疾病进展和开发时序性治疗策略具有重要意义。

#### 二、创新性特色

##### 1. 整合多组学与比较分析：

- 文章通过比较不同研究中 SG 的 mRNA 和蛋白质组成，指出 SG 成分具有高度细胞类型、应激类型和实验方法的依赖性，挑战了“通用 SG 组成”的传统观念，强调 SG 功能的上下文依赖性。

##### 2. 提出 SG 在无应激条件下的生理功能：

- 传统认为 SG 仅在应激条件下形成，本文指出 SG 核心成分在无应激条件下也存在并可能发挥功能，拓展了 SG 的生理意义。

##### 3. 揭示 SG 在神经再生中的新机制：

- 特别强调了 G3BP1 等 SG 蛋白在轴突再生中的调控作用，提出了“轴突 SG”概念，并揭示了其通过调控局部翻译影响神经再生能力。

##### 4. 探讨 SG 作为信号枢纽的机制：

- 提出 SG 不仅是 mRNA 的储存库，更是细胞信号通路的调控中心，通过隔离关键信号分子（如激酶、mRNA）影响 MAPK、NF- $\kappa$ B、p53 等通路。

#### 三、对学科的启示

##### 1. 推动 SG 研究从“静态结构”向“动态功能”转变：

- 文章强调 SG 的动态组装与解聚对其功能的关键影响，呼吁未来研究更多关注 SG 的时间维度与空间调控。

##### 2. 为疾病机制与治疗提供新靶点：

- SG 成分（如 G3BP1、TIA1、TDP-43）在多种疾病中突变或异常积累，提示 SG 可作为神经退行性疾病、癌症、病毒感染等的潜在治疗靶点。

##### 3. 倡导标准化与上下文驱动的研究方法：

- 文章指出当前 SG 研究因方法、细胞类型和应激条件不同而存在较大差异，呼吁建立标准化分析流程，并提倡在特定病理或生理背景下研究 SG。

##### 4. 促进跨学科融合：

- SG 研究涉及细胞生物学、神经科学、病毒学、癌症生物学和免疫学等多个领域，本文的综述有助于促进各领域之间的交叉融合，推动对 SG 功能的全面理解。

总结：本文是一篇具有高度系统性和前瞻性的综述，不仅总结了 SG 在细胞应激响应中的经典角色，更拓展了其在生理稳态、神经再生、免疫调节和疾病发生中的新功能。其创新之处在于强调 SG 的动态性、上下文依赖性与多功能性，并为未来研究指明了方向——尤其是在疾病机制解析与靶向治疗开发方面具有重要启示意义。