Invited Mini Review

Stress granules dynamics: benefits in cancer

*Jeong In Lee & Sim Namkoong**

Department of Biochemistry, Kangwon National University, Chuncheon 24341, Korea

Stress granules (SGs) are stress-induced subcellular compartments, which carry out a particular function to cope with stress. These granules protect cells from stress-related damage and cell death through dynamic sequestration of numerous ribonucleoproteins (RNPs) and signaling proteins, thereby promoting cell survival under both physiological and pathological condition. During tumorigenesis, cancer cells are repeatedly exposed to diverse stress stimuli from the tumor microenvironment, and the dynamics of SGs is often modulated due to the alteration of gene expression patterns in cancer cells, leading to tumor progression as well as resistance to anticancer treatment. In this mini review, we provide a brief discussion about our current understanding of the fundamental roles of SGs during physiological stress and the effect of dysregulated SGs on cancer cell fitness and cancer therapy. [BMB Reports 2022; 55(12): 577-586]

INTRODUCTION

Cells are constantly exposed to diverse stress stimuli such as osmotic stress, oxidative stress, heat shock, cold shock, endoplasmic reticulum (ER) stress, and pharmacological treatment (1, 2). These internal and external stimuli are often harmful to cells. Therefore, cells have to develop strategies to overcome such stress stimuli. For instance, once cellular stress disrupts homeostatic balance, multiple defense mechanisms including control of gene expression can be triggered to avoid cell death and cellular malfunctioning. Stress granules (SGs) are prominent cytoplasmic ribonucleoprotein (RNP) granules during stress. These granules are considered as evolutionarily conserved cellular defense mechanisms against to various stresses (3). SGs sequester certain transcripts and proteins from the soluble portion of cytoplasm during physiological stress (4-6). This could be a stress response mechanism to regulate gene expression and cellular signaling. SGs are dynamically regulated depending on the type of cells and stress. They can affect cell fate such as cell growth, apoptosis, and senescence (7). Their modulation is often associated with age-associated human diseases including neurodegenerative disease and cancer (7). In particular, cancer cells are inevitably exposed to severe stressful environment during tumorigenesis and anticancer treatment. Accordingly, there is increasing evidence suggesting that alteration of SGs formation can protect cancer cells from apoptosis, leading to drug resistance. This mini review aims to provide an updated signaling molecular network regarding effects of SGs on cancer and cancer drug resistance. Potential roles of SGs in cancer therapy are also discussed.

SIGNALING PATHWAYS FOR SGs ASSEMBLY

SGs are dynamically regulated (8). These granules form in cytoplasm during stress and usually disappear after recovery from the stress. In addition, SGs formation can be triggered by diverse conditions. The molecular mechanism of SGs assembly can be different depending on stress types (Table 1).

SGs assembly is typically connected with translation inhibition (9). When translation is suppressed, translating ribosomes will run off their mRNAs. These naked mRNAs can bind to RNA-binding proteins which can be favorably incorporated into SGs (10). Although diverse stimuli can activate different stress-sensing kinases including general control nonderepressible 2 (GCN2), protein kinas R (PKR), protein kinase R-like endoplasmic reticulum kinase (PERK), and heme-regulated inhibitor (HRI), they commonly phosphorylate eukaryotic translation initiation factor 2 subunit alpha (eIF2α) at serine 51 (Fig. 1) (11, 12). Although phosphorylation of eIF2α is considered as one of key regulatory events for both SGs formation and translation inhibition (13, 14), SGs formation can be induced regardless of eIF2α phosphorylation (15). Once eIF4F complex containing eIF4A, eIF4E, and eIF4G is disrupted, SGs assembly can be promoted without eIF2α phosphorylation (Fig. 1) (15). For instance, pharmacological inhibitors of RNA helicase eIF4A such as 15-deoxy-Δ (12,14)-prostaglandin J2 and pateamine A can bind to eIF4A and dissociate eIF4A-eIF4G interaction (16, 17). In addition, sodium selenite can disrupt the association of eIF4E and eIF4G (18). In short, SGs formation can be mediated by either eIF2α phosphorylation or eIF4F complex dissociation (Fig. 1).

The mechanistic target of rapamycin (mTOR) signaling is also engaged in the regulation of SGs assembly. mTOR is a serine/threonine kinase controlling cell growth, survival, and

Table 1. Stress conditions and cancer drugs that promote SGs assembly

Inducer	Category	Mechanism	Cell line (concentration and time)	References
Sodium arsenite	Oxidative stress	Inducing eIF2α phosphorylation	HeLa (0.5 mM for 30 min), DU145 and COS-7 (0.5 mM for 30 min)	(78, 79)
Sorbitol	Osmotic stress, oxidative stress	Inducing eIF2α phosphorylation	HEK293T (0.4 M for 1 h)	(80)
Hydrogen peroxide	Oxidative stress	Disrupting eIF4F complex	U2OS (1 mM for 2 h)	(81)
Sodium selenite	Oxidative stress	Disrupting eIF4F complex	U2OS (1 mM for 2 h)	(18)
Malonate	Mitochondrial stressor (oxidative stress, energy depletion)	Inducing 4EBP1 dephosphorylation	HeLa (50 nM for 1 h)	(82)
NaCl	Osmotic stress	Phase separation	U2OS (0.2 M for 1 h)	(81)
Carbonyl cyanide (trifluoromethoxy) phenylhydrazone (FCCP)	Mitochondrial stressor (oxidative stress, energy depletion)	Inducing eIF2α phosphorylation	HeLa (1 µM for 1.5 h)	(83)
Thapsigargin	ER stress	Inducing eIF2α phosphorylation	HEK293 and NIH3T3 (1 µM for 1.5 h)	(5)
Dithiothreitol (DTT)	ER stress	Inducing eIF2α phosphorylation	HeLa (1 mM for 1 h)	(84)
Lactacystin	Proteasome inhibitor	Inducing eIF2α phosphorylation	HeLa (10 µM for 4 h)	(85)
MG132	Proteasome inhibitor	Inducing eIF2α phosphorylation	HeLa (0.1 mM for 3 h), U2OS (10 µg/ml for 1 h)	(81, 85, 86)
Edeine	Protein synthesis inhibitor	Preventing 60S binding to the 48S complex	Oligodendrocytes (0.1 mM for 6 h)	(87)
Sodium azide	Mitochondrial stressor	eIF2α-independent mechanism	BY4741 (0.5 % (v/v) for 30 min)	(88)
Clotrimazole	Mitochondrial stressor	Inducing eIF2α phosphorylation	Human vascular smooth muscle cell (VSMC) (20 µM for 45 min)	(89)
Hippuristanol	Natural product	Inactivating eIF4A	U2OS (1 µM for 1 h)	(90)
Boric acid	Inorganic compound	Inducing eIF2α phosphorylation	DU-145 (50 µM for 1 h-3 h)	(91)
Pateamine A	Natural product	Inactivating eIF4A	HeLa (50 nM for 30 min), A549 (20 nM for 1 h), U2OS (0.4 M for 1 h)	(17, 81, 90)
Deoxy-delta12,14-prostaglandin J2 (15d-PGJ2)	Natural product	Inactivating eIF4A	HeLa (50 µM for 0.5 h), DLD1 (50 µM for 1 h)	(72, 77)
Rocaglamide A	Natural product	Inactivating eIF4A	U2OS (1 µM for 1 h)	(81)
UV irradiation	DNA damage	Inducing eIF2α phosphorylation	U2OS (10 or 20 mJ/cm for 2 h)	(92, 93)
Heat shock	Protein denaturation	Inducing eIF2α phosphorylation	HeLa (43.5°C for 45 min)	(86)
Cold shock	Low temperature stress	Inducing eIF2α phosphorylation	COS7(10°C for 10 h)	(2)
Bortezomib	Proteasome inhibitor	Inducing eIF2α phosphorylation	HeLa (1 µM for 3 h), U2OS (25 µM for 4 h)	(69, 94)
Sorafenib	Proteasome inhibitor	Inducing eIF2α phosphorylation	Hep3B, HuH-7 (10 µM for 2 h)	(95)
Paclitaxel	Microtubule stabilizer	Promoting microtubule assembly and stabilization	U2OS (400 µM for 1 h)	(96)
Vinorelbine	Microtubule disruption	Inducing eIF2αphosphorylation and 4EBP1 dephosphorylation	U2OS (150 µM for 1 h)	(96, 97)
Vinblastine	Microtubule disruption	Inducing eIF2α phosphorylation and 4EBP1 dephosphorylation	U2OS (300 µM for 1 h)	(96)
Vincristine	Microtubule disruption	Inducing eIF2α phosphorylation and 4EBP1 dephosphorylation	U2OS (750 µM for 1 h)	(96)
Oxaliplatin	DNA damage	Inducing eIF2α phosphorylation	U2OS (600 µM, 2 mM for 4 h)	(97)
Cisplatin	DNA damage	Inducing eIF2α phosphorylation	Glioma C6, U87MG (5 mM for 2 h), U2OS (250 µM for 4 h)	(97, 98)
Carboplatin	DNA damage	Inducing eIF2α phosphorylation	U2OS (10 mM for 4 h)	(97)
Fluorouracil (5-FU)	Incorporation into DNA and RNA	Inducing eIF2α phosphorylation	HeLa (0.1 mM for 72 h)	(70)
6-Thioguanine	Incorporation into DNA and RNA	Inducing eIF2α phosphorylation	HeLa (10 µM for 72 h)	(70)
5-Azacytidine	Incorporation into DNA and RNA	Inducing eIF2α phosphorylation	HeLa (50 µM for 72 h)	(70)
Etoposide	Topoisomerase II inhibitor	Inducing eIF2α phosphorylation	glioma C6, U87MG (50 µM for 2 h)	(98)
Lapatinib	Tyrosine kinase inhibitor	Inducing eIF2α phosphorylation	T47D (20 mM for 2h)	(72)
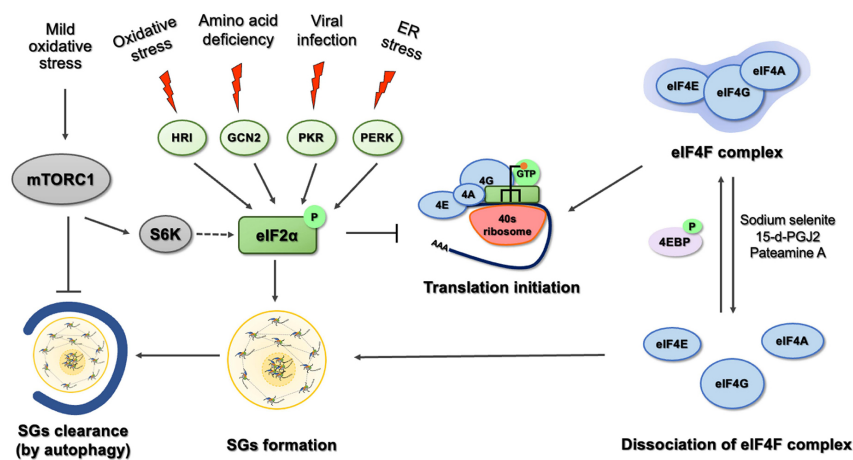
Fig. 1. Signaling pathways engaged in SGs formation. Once cells are exposed to diverse stresses, eIF2α can be phosphorylated by stress-sensing kinases (HRI, GCN2, PKR and PERK). Phosphorylated eIF2α inhibits translation initiation and triggers assembly of SGs. On the other hand, SGs assembly can be induced independently of eIF2α phosphorylation. When the eIF4F (eIF4A-eIF4E-eIF4G) complex is dissociated, translation inhibition occurs, thereby promoting assembly of SGs. Finally, mTORC1 contributes to increase SGs formation. In brief, during mild oxidative stress, mTORC1 can induce assembly of SGs through promoting eIF2α phosphorylation, and mTORC1 can increase persistence of SGs through inhibiting autophagy which regulates SGs clearance.

metabolism. It functions as the catalytic subunit of two distinct protein complexes, mTORC1 and mTORC2, which are evolutionarily conserved in all eukaryotes (19). mTORC1 complex consists of mTOR, regulatory associated protein of mTOR (RAPTOR), proline-rich AKT substrate 40 kDa (PRAS40), and mammalian lethal with sec-13 protein 8 (mLST8). Downstream targets of mTORC1 are numerous proteins involved in the regulation of translation, including eIF4E binding protein (4EBP) and 70 kDa ribosomal S6 Kinase (S6K) (19). Activated mTORC1 complex can phosphorylate 4EBP to dissociate from eIF4E, stimulating translation initiation (19). Once mTORC1 is suppressed, unphosphorylated 4EBP can bind to eIF4E, which results in inhibition of both eIF4F complex assembly and translation initiation (19). Several SGs inducers such as H_2O_2, cold shock, and selenite promote dephosphorylation of 4EBP, and the inhibition of eIF4E-4EBP complex by genetic intervention impairs SGs formation (2, 18, 20). Therefore, mTORC1 inhibition was supposed to enhance SGs formation.

However, it is unclear whether SGs formation mediated by the eIF4E-4EBP complex depends on mTORC1 inactivation. Currently, there is no experimental evidence to show that mTOR inhibition is sufficient to induce SGs formation (21, 22). Although it is somewhat paradoxical, there is growing evidence showing that mTORC1 is required for the formation of SGs (21, 23, 24). Several studies have demonstrated that SGs formation is reduced through inhibition of mTORC1 or S6K using pharmacological treatment or genetic depletion during arsenic toxicity and heat shock stress (21, 23). Furthermore, various stress stimuli can activate mTORC1 through PI3K and p38, thus enhancing the formation of SGs (24). Although the exact mechanism of how mTORC1 promotes SGs formation needs

to be studied further, two possible mechanisms can be suggested based on current knowledge and evidence (Fig. 1). First, activated mTORC1 can promote phosphorylation of eIF2α through S6K during mild stress (21), which can enhance SGs assembly. Second, SGs can be cleared by autophagy (25) which can be blocked by mTORC1 (19). In other words, mTORC1 activation may increase SGs persistence through autophagy inhibition.

COMPONENTS AND FUNCTIONS OF SGs

Recent studies suggest that SGs have a biphasic structure with core structures surrounded by shell layers (4, 26, 27). Such a core structure is thought to be more stable while components in the shell layer are transient and dynamically regulated. This section discusses which biomolecules are more preferentially incorporated into SGs and how these SGs-targeted molecules can affect various cell signaling pathways.

Proteins
SGs formation can be induced by various physiological stress, but the signaling pathways involved in the formation of SGs are closely linked to translation inhibition (4, 26, 27). Upon translation inhibition, exposed RNAs initially bind to RNA-binding proteins containing intrinsically disordered regions (IDRs) such as poly(A)-binding protein 1 (PABP1), T-cell internal antigen 1 (TIA1), and Ras-GTPase-activating protein SH3-domain-binding protein1 (G3BP1). These molecules termed as SGs-nucleating proteins subsequently combine with each other to initiate the assembly of SGs through liquid-liquid phase separation (LLPS), thereby generating the core structures of SGs. Additional proteins and transcripts can be further incorporated

into the shell layers of SGs through protein-protein, protein-RNA, and RNA-RNA interactions during maturation of SGs (28). Thus, regulatory factors regarding these interactions in addition to phase separation can also affect functions of SGs by modulating components of SGs. Recent evidence indicates that SGs have more active roles in metabolism, stress signaling, and cell fate decision such as apoptosis and cellular senescence (Fig. 2) (7, 29).

For instance, during severe stress such as X-rays and genotoxic drugs, the receptor of activated protein C kinase 1 (RACK1) protein can bind to stress-responsive MAP three kinase 1 (MTK1) and enhances its activation, leading to apoptosis (30). During stress, SGs can sequester RACK1, thereby suppressing apoptosis. Similarly, sequestration of RAPTOR into SGs can prevent mTORC1-hyperactivation-induced apoptosis by inhibiting mTORC1 association (31). As mentioned in the former section, mTORC1 activation in response to stress stimuli can enhance formation of SGs. Enhanced SGs can inversely suppress mTORC1 activity. This could be also one of the negative feedback mechanisms for maintaining the balance of SGs during stress, which affects cell survival.

Meanwhile, SGs formation is also related to cellular senescence. In sodium butyrate or lopinavir-induced senescent cell model, SGs formation is impaired by depletion of transcription factor SP1, which regulates expression levels of G3BP and TIA-1/TIAR (32). Consistent with these observations, a recent study has shown that repeated exposure to stress can induce SGs in proliferative or pre-senescent cells, but not in fully senescent cells (33). Conversely, formation of SGs is sufficient to decrease cellular senescence. SGs sequester plasminogen activator inhibitor-1 (PAI-1), an established promoter of senescence, and decrease PAI-1 secretion, leading to upregulation of nuclear cyclin D1 which promotes cell cycle progression (33).

Transcripts

Besides signaling proteins, transcripts are also regulated by formation of SGs. Cytoplasmic RNA sequestration into SGs was thought to be a simple consequence of global translation suppression (34). However, characterization of the SGs transcriptome has revealed that only a small subset of translationally suppressed mRNAs is incorporated into SGs upon stress (5, 6). In addition, a recent study using single-molecular imaging of mRNA translation has demonstrated that translating mRNA can also enter and localized to SGs, although non-translating mRNAs are more enriched in SGs (35), indicating that translation suppression is not the sole mechanism for SGs-enrichment. According to transcriptomic analyses, the most prominent features identified in SGs RNAs are extended transcript length and specific RNA motifs such as adenylate-uridylate (AU)-rich elements (5, 6). SGs-targeted transcripts are conserved across distinct stress conditions and highly enriched with proto-oncogenes (5), suggesting that SGs targeting of RNAs might provide an additional mechanism underlying the intricate gene regulation of cell survival and proliferation under stressful conditions.

Besides specific RNA sequence elements, RNA modification can also affect the sequestration of transcripts into SGs (36, 37). N^6-methyladenosine (m^{6}A), the most prevalent internal modification on mRNA, can regulate mRNA stability (38). It has been demonstrated that mRNAs containing multiple, but not single, m^{6}A residues can enhance phase separation by binding to YTHDF proteins. These poly-methylated mRNAs exhibit higher levels of SGs enrichment than non-methylated or mono-methylated mRNAs in NIH3T3 mouse fibroblast cells. The number of m^{6}A nucleotides is correlated with SGs enrichment regardless of transcript length (36). Likewise, m^{6}A-modifed RNAs are highly enriched in U2OS human osteosarcoma cells, facilitating SGs formation through interaction with YTHDF proteins (37). These findings collectively suggest that m^{6}A modification might modulate SGs targeting of RNAs. However, a recent study has found that m^{6}A modifications have limited effects on mRNA recruited into SGs (39). Thus, the relationship of m^{6}A modification with SGs targeting remains to be elucidated.
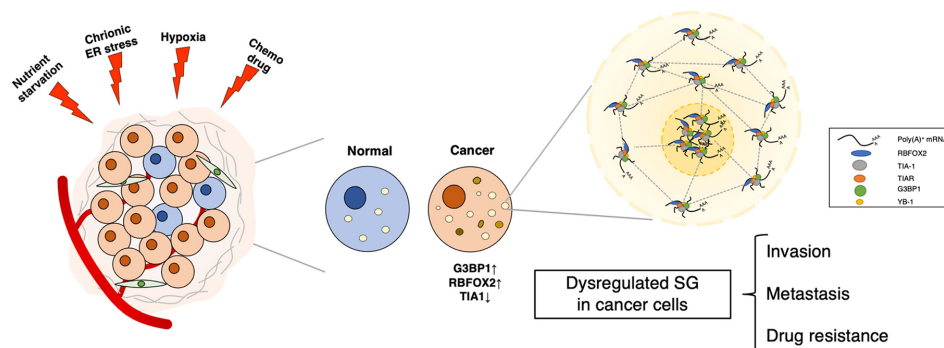
Fig. 2. An overview of the effect of tumor-associated stress and SGs in cancer cells during tumor progression. In various cancer cells, SGs formation is typically dysregulated due to tumor microenvironment and genetic alteration. Such modulation of SGs can promote cancer progression and anticancer drug resistance.

SGs AND CANCER

During tumorigenesis, cancer cells face harsh environmental stresses such as nutrient starvation, hypoxia, and oxidative stress. Protein synthesis to satisfy proliferative demand often causes chronic ER stress due to limited ER capacity under these stressful conditions. Thus, perhaps not surprisingly, SGs are often detected in tumor tissues. They are closely related to cancer cell survival and progression (Fig. 2). This section discusses how cancer cells modulate SGs formation, and how these modulated SGs affect cancer cell development.

SGs-targeted proteins and cancer progression

G3BP1 is a critical SGs nucleator. Its overexpression is sufficient to induce SGs formation even without stress stimuli while its depletion reduces SGs under stress (40-42). G3BP1 is involved in various cellular processes controlling cell survival, migration, and invasion. Elevated expression of G3BP1 is frequently observed in various cancers including colon cancer, sarcoma, and non-small cell lung cancer (NSCLC), contributing to tumor progression and metastasis (43-45). Depletion of G3BP1 can reduce cancer cell proliferation, invasion, and metastatic potential (43, 44).

Y-box protein 1 (YB-1) protein is a component of SGs. It can directly bind to *G3BP1* mRNA and upregulate its translation, thereby promoting assembly of SGs (46). In human sarcoma, YB-1 expression is correlated with G3BP1 level. It is linked to poor outcome of cancer patients (46). Elevated expression of both G3BP1 and YB1 proteins is positively correlated with the clinical stage of NSCLC (47). Consistent with this, MS-275, a class I HDAC inhibitor, can reduce sarcoma metastasis by promoting YB-1 acetylation which inhibits binding and translational activation of its target *G3BP1* mRNA (48).

RBP fox-1 homolog 2 (RBFOX2) is an RNA binding protein that can regulate RNA metabolic processes including alternative splicing. Upon stress, RBFOX2 targeted to SGs is more likely to bind to cell cycle-related mRNAs (49). The most prominent target of RBFOX2 is retinoblastoma 1 (*RB1*) mRNA which encodes a negative cell cycle regulator. RBFOX2 can block RB1 mRNA translation through sequestration into SGs. It can also promote cell cycle progression under stress (49). RB1 expression is negatively correlated with RBFOX2 level in human colon cancer cells (50). Dissociation of RBFOX2 from SGs through resveratrol treatment can inhibit cancer progression in a mouse melanoma model (50).

Reactive oxygen species (ROS) has a dual role in cancer. ROS can promote cancer cell proliferation and survival, whereas oxidate stress induced by ROS can trigger cancer cell death. TIA-1 is thought to be an important tumor suppressor. Several studies have shown that depletion of TIA-1 can promote cell proliferation while overexpression of TIA-1 exhibits an opposite effect and induces cell cycle arrest (51-53). Lower expression levels of TIA1 protein have been observed in colon cancer tissues than in normal tissues (54). ROS such as H_2O_2 can oxidize TIA-1, which impairs formation of SGs and makes cells become more sensitive to stress-induced apoptosis (55). These results suggest that oxidation of TIA-1 is one of tumor suppressive mechanisms through ROS during tumorigenesis.

Histone deacetylase 6 (HDAC6) is a cytosolic deacetylase that can regulate microtubule dynamics through α-tubulin deacetylation and interactions with ubiquitinated proteins (56). During stress, HDAC6 can be localized in SGs through binding to G3BP (57). G3BP1 dephosphorylation is triggered by various stresses, which increase its binding affinity to HDAC6 (40, 57, 58). Deacetylated G3BP1 by HDAC6 can stably bind to RNAs including *c-Myc* mRNA and *Tau* mRNAs, thereby promoting interaction with PABP1, a key component of SGs (58). HDAC6 is overexpressed in many types of cancer, promoting proliferation and tumorigenesis (56, 59). Increased level of HDAC6 possibly alters SGs dynamics, which is critical for cancer cell survival during stress through RNA binding activity of G3BP1.

SGs between cellular signaling and cancer progression

mTORC1 can promote cell growth, proliferation, and metabolism. Several studies have shown that mTORC1 activation in cancer cells can facilitate SGs assembly while mTORC1 inhibition can reduce SGs formation in cellular stress (21, 23). Conversely, assembly of SGs can inhibit mTORC1 activity through sequestration of its components, mTOR and RAPTOR (60). Dual specificity tyrosine phosphorylation-regulated kinase 3 (DYRK3) and chaperone heat shock protein 90 (Hsp90) contribute to mTORC1 regulation by regulating disassembly of SGs (60, 61). Upon stress, DYRK3 dissociates from Hsp90 and then enters SGs, promoting SGs assembly and mTORC1 inhibition. After stress relief, DYRK3 interacts with Hsp90 to be stabilized and eventually active. Active DYRK3 promotes disassembly of SGs, and mTORC1 signaling is restored. Regardless of SGs formation, activated DYRK3 can phosphorylate PRAS40 to abolish its inhibitory effect on mTOR.

Hsp90 activity can be regulated by HDAC6 which deacetylates Hsp90 and promotes its chaperon function. HDAC6 inhibition exhibits an antileukemic activity through hyperacetylation of Hsp90, which promotes the degradation of oncoproteins such as Bcr-Abl, AKT and c-Raf (62). Although whether HDAC6 expression is correlated with Hsp90 remains unclear, Hsp90 expression is elevated in various types of cancer and is thought to contribute to cancer cell proliferation (63-65). Moreover, this upregulated chaperone in cancer cells might provide a mechanism that supports rapid mTORC1 reactivation through disassembly of SGs during stress recovery.

RAS signaling regulates various biological processes such as cell growth, proliferation, and differentiation in response to external growth factors. Constitutively active forms of three RAS (KRAS, NRAS, and HRAS) due to missense mutation are frequently detected in human cancers (66). Oncogenic RAS contributes to induction of various stresses such as hypoxia, oxidative and ER stress, and replicative stress, which are associated with tu-

morigenesis (67). Cell stress is required to promote cellular transformation. It can lead to cell death once it is excessive. However, oncogenic RAS activation provides stress-adaptive mechanisms to avoid cell death, thereby facilitating tumorigenesis.

SGs more rapidly forms in mutant HRAS-transformed fibroblasts than in non-transformed fibroblasts (40). In human colon and pancreatic cancer cell lines, mutant KRAS showed markedly upregulated SGs formation than wild-type (WT) KRAS upon various cellular stress including oxidative stress, UV-C stress, and chemotherapeutic drug-induced stress. This enhanced formation of SGs can be revoked by depletion of KRAS, indicating that mutant KRAS is required for upregulation of SGs (68). SGs were also detected in mutant KRAS pancreatic tumor tissues, but not in WT KRAS tumors tissues in the absence of external stress stimuli, suggesting that mutant KRAS might modulate SGs formation through stimulation of additional stress responsive signaling.

Upregulation of SGs in mutant KRAS cells is mediated by eIF4A inactivation. Mutant KRAS can stimulate the production of 15-deoxy-delta 12,14-prostaglandin J2 (15-d-PGJ2), an eIF4A inhibitor, through two distinct mechanisms (68). Shortly, mutant KRAS can upregulate cyclooxygenase (COX) which catalyzes prostaglandin biosynthesis, while mutant KRAS signaling downregulates NAD$^+$-dependent 15-hydroxyprostaglanding dehydrogenase (HGPD) which promotes prostaglandin degradation. 15-d-PGJ2 is a secreted molecule. It can stimulate SGs formation in an autocrine manner as well as in a paracrine manner when cells are exposed to stress stimuli, blocking stress-induced cell death (68). In other words, secreted 15-d-PGJ2 from mutant KRAS cells can promote cell survival through SGs upregulation in both WT and mutant KRAS cells in response to diverse stress stimuli from the tumor microenvironment and chemotherapeutic reagents.

SGs AND CANCER TREATMENT

Cancer cells eventually acquire anticancer drug resistance after therapy, leading to cancer recurrences and failure of cancer treatment. It has been reported that several chemotherapeutic reagents can induce SGs formation, which can cause resistance to cancer cell death (Tables 1, 2).

Bortezomib, a proteasomal inhibitor, can promote assembly of SGs through HRI-mediated eIF2α phosphorylation in cancer cells (69). Depletion of HRI can abolish bortezomib-induced SGs formation, sensitizing cancer cells to bortezomib. Mechanistically, bortezomib-induced SGs can sequester and destabilize mRNA of p21, a cyclin-dependent kinase inhibitor, thus suppressing apoptosis and promoting drug-resistance.

Treatment with 5-fluorouacil (5-FU) can trigger PRK-mediated elf2α phosphorylation, increasing SGs formation dose-dependently (70). It has been proposed that receptor for activated C kinase 1 (RACK1) can mediate SGs-induced resistance to 5-FU. RACK1 is thought to have a pro-apoptotic function. 5-FU-induced SGs can sequester RACK1. Similarly, morusin, a cytotoxic drug, can induce SGs formation through PKR-eIF2α phosphorylation (71). G3BP1 depletion can increase cancer cell death in response to morusin, releasing RACK1 from SGs. Besides chemotherapeutic agents, lapatinib, a HER2/ERBB2-targeting drug, can induce SGs formation through PERK pathway (72). PERK depletion can abolish lapatinib-induced SGs assembly and sensitize breast cancer cells to lapatinib, increasing cell death. Collectively, these results indicate that blocking assembly of SGs can enhance the anticancer effect of either chemotherapy or targeted therapy. Meanwhile, dysregulated SGs dynamics contributes to avoiding apoptosis and eventually eliciting chemotherapeutic agent resistance during chemotherapy (Table 2).

Speckle-type BTB/POZ protein (SPOP), an E3 ubiquitin ligase adaptor, is commonly mutated in prostate cancer (73). SPOP can facilitate ubiquitin-dependent degradation of Caprin1. SGs formation is promoted by physical interaction between Caprin1 and G3BP1. Caprin1 expression is elevated in SPOP mutant

Table 2. SGs-mediated chemotherapy resistance

Chemotherapeutic reagent	Cancer cell type	Mechanism of drug resistance via SGs formation	References
Bortezomib	Lung cancer Colorectal cancer	Sequestration of *p21* (cyclin-dependent kinase inhibitor) mRNA into SGs	(69, 99)
5-fluorouacil (5-FU)	Cervical cancer	Sequestration of RACK1 (pro-apoptotic protein) into SGs	(70)
Docetaxel	Prostate cancer	SPOP mutation Caprin1 overexpression	(73)
Cisplatin	Cervical cancer	*G3BP1* overexpression (*G3BP1* mRNA ↑)	(74)
Paclitaxel	Cervical cancer	*G3BP1* overexpression (*G3BP1* mRNA ↑)	(74)
Oxaliplatin	Pancreatic cancer Colorectal cancer	Upregulation of 15-d-PGJ2 by KRAS mutation	(68)
	Gastric cancer	*G3BP1* overexpression (*G3BP1* mRNA ↑)	(76)
Capecitabine	Gastric cancer	*G3BP1* overexpression (*G3BP1* mRNA ↑)	(76)

prostate cancer cell line, thereby upregulating SGs formation which leads to resistance to docetaxel-induced cell death (73). In contrast, Caprin1 depletion increases sensitivity to cell death in stress conditions including docetaxel and suppresses tumor growth in mouse xenograft models (73).

Hypoxia can alter cancer cell metabolism, leading to therapeutic resistance. In human cervical cancer HeLa cells, hypoxia can trigger eIF2α phosphorylation and SGs formation (74). HeLa cells are more sensitive to both cisplatin and paclitaxel in normoxia than in a hypoxic condition. β-estradiol, progesterone, and stanolone can suppress hypoxia-induced formation of SGs, increasing sensitivity to cisplatin and paclitaxel under hypoxia but not under normoxia (74). In addition, G3BP1 overexpression can abolish effects of β-estradiol, progesterone, and stanolone, restoring formation of SGs and chemodrug resistance during hypoxia. On the other hand, raloxifene, a selective estrogen receptor modulator, delays disassembly of hypoxia-induced SGs during post-hypoxia in primary glioma cells (75). SGs usually disappear within 15 min post-hypoxia. In contrast, SGs persists up to 2 hours in cells pre-treated with raloxifene (75). This delayed clearance of SGs is abolished after depleting G3BP1 and G3BP2 (75), indicating that G3BPs are required for raloxifene-induced persistence of SGs. These results collectively indicate that the dynamics of the SGs assembly is important for resistance to cancer cell death.

In gastric cancer patients, high G3BP1 expression levels are correlated with poor outcomes such as tumor progression, invasion and metastasis (76). In addition, G3BP1 expression is significantly associated with poor survival of patients receiving postoperative chemotherapy (76). G3BP1 silencing can sensitize gastric cancer cells to chemotherapeutic agents such as oxaliplatin and capecitabine, suppressing chemodrug-induced formation of SGs. In response to chemodrug treatment, G3BP1 can reduce mRNA stability of *Bax*, a pro-apoptotic gene. It can also interact with YWHAZ to sequesters Bax protein in gastric cancer cells, thereby suppressing apoptosis (76). In addition, G3BP1 depletion can increase the sensitivity of lung cancer cells to radiation-induced cell death (although assembly of SGs has not been observed yet in response to radiation) by impairing DNA repair with elevated ROS levels (77). These studies collectively suggest that G3BP1 can be a promising target for overcoming therapeutic resistance to chemotherapy and radiation.

SUMMARY

SGs form under diverse stress conditions in the cytosol. SGs formation was thought to be a simple consequence of translation suppression. However, for more than a decade, many studies have revealed that some proteins and transcripts are specifically targeted to SGs. SGs targeting of certain protein and transcripts is closely linked to cellular adaptation to stress. Once SGs formation is upregulated, more pro-apoptotic proteins are sequestered into SG, thereby blocking apoptosis. In addition, SGs formation has active roles in enhancing tumor cell fitness.

High expression of SGs-nucleating proteins such as G3BP1 can promote SGs assembly. Thus, G3BP expression is often positively associated with cancer progression, invasion, and metastasis, contributing to poor outcomes of cancer patients. SGs formation is promoted in response to tumor microenvironment such as hypoxia and paracrine secretion of the prostaglandin as well as several chemotherapeutic drugs, leading to resistance to cell death. Many studies have shown that high abundance of SGs can inhibit apoptosis and promote anticancer drug resistance, whereas dysregulated dynamics of SGs such as interfering SGs disassembly can block cancer cell death during cancer drug treatment. Therefore, targeting SGs can be a promising therapeutic strategy for cancer treatment by increasing cancer cell sensitivity to anticancer drugs.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Anderson P and Kedersha N (2009) Stress granules. Curr Biol 19, R397-398
2. Hofmann S, Cherkasova V, Bankhead P, Bukau B and Stoecklin G (2012) Translation suppression promotes stress granule formation and cell survival in response to cold shock. Mol Biol Cell 23, 3786-3800
3. Mahboubi H and Stochaj U (2017) Cytoplasmic stress granules: dynamic modulators of cell signaling and disease. Biochim Biophys Acta Mol Basis Dis 1863, 884-895
4. Jain S, Wheeler JR, Walters RW, Agrawal A, Barsic A and Parker R (2016) ATPase-modulated stress granules contain a diverse proteome and substructure. Cell 164, 487-498
5. Namkoong S, Ho A, Woo YM, Kwak H and Lee JH (2018) Systematic characterization of stress-induced RNA granulation. Mol Cell 70, 175-187 e8
6. Khong A, Matheny T, Jain S, Mitchell SF, Wheeler JR and Parker R (2017) The stress granule transcriptome reveals principles of mRNA accumulation in stress granules. Mol Cell 68, 808-820 e5
7. Cao X, Jin X and Liu B (2020) The involvement of stress granules in aging and aging-associated diseases. Aging Cell 19, e13136
8. Protter DSW and Parker R (2016) Principles and properties of stress granules. Trends Cell Biol 26, 668-679
9. Ivanov P, Kedersha N and Anderson P (2019) Stress granules and processing bodies in translational control. Cold Spring Harb Perspect Biol 11, a032813
10. Lee CY and Seydoux G (2019) Dynamics of mRNA entry

into stress granules. Nat Cell Biol 21, 116-117

11. Anderson P and Kedersha N (2002) Visibly stressed: the role of eIF2, TIA-1, and stress granules in protein translation. Cell Stress Chaperones 7, 213-221

12. Wek RC, Jiang HY and Anthony TG (2006) Coping with stress: eIF2 kinases and translational control. Biochem Soc Trans 34, 7-11

13. Kedersha NL, Gupta M, Li W, Miller I and Anderson P (1999) RNA-binding proteins TIA-1 and TIAR link the phosphorylation of eIF-2 alpha to the assembly of mammalian stress granules. J Cell Biol 147, 1431-1442

14. Kedersha N, Chen S, Gilks N et al (2002) Evidence that ternary complex (eIF2-GTP-tRNA(i)(Met))-deficient preinitiation complexes are core constituents of mammalian stress granules. Mol Biol Cell 13, 195-210

15. Mazroui R, Sukarieh R, Bordeleau ME et al (2006) Inhibition of ribosome recruitment induces stress granule formation independently of eukaryotic initiation factor 2alpha phosphorylation. Mol Biol Cell 17, 4212-4219

16. Kim WJ, Kim JH and Jang SK (2007) Anti-inflammatory lipid mediator 15d-PGJ2 inhibits translation through inactivation of eIF4A. EMBO J 26, 5020-5032

17. Dang Y, Kedersha N, Low WK et al (2006) Eukaryotic initiation factor 2alpha-independent pathway of stress granule induction by the natural product pateamine A. J Biol Chem 281, 32870-32878

18. Fujimura K, Sasaki AT and Anderson P (2012) Selenite targets eIF4E-binding protein-1 to inhibit translation initiation and induce the assembly of non-canonical stress granules. Nucleic Acids Res 40, 8099-8110

19. Saxton RA and Sabatini DM (2017) mTOR signaling in growth, metabolism, and disease. Cell 168, 960-976

20. Emara MM, Fujimura K, Sciaranghella D, Ivanova V, Ivanov P and Anderson P (2012) Hydrogen peroxide induces stress granule formation independent of eIF2alpha phosphorylation. Biochem Biophys Res Commun 423, 763-769

21. Sfakianos AP, Mellor LE, Pang YF et al (2018) The mTOR-S6 kinase pathway promotes stress granule assembly. Cell Death Differ 25, 1766-1780

22. Cadena Sandoval M, Heberle AM, Rehbein U, Barile C, Ramos Pittol JM and Thedieck K (2021) mTORC1 crosstalk with stress granules in aging and age-related diseases. Front Aging 2, 761333

23. Fournier MJ, Coudert L, Mellaoui S et al (2013) Inactivation of the mTORC1-eukaryotic translation initiation factor 4E pathway alters stress granule formation. Mol Cell Biol 33, 2285-2301

24. Heberle AM, Razquin Navas P, Langelaar-Makkinje M et al (2019) The PI3K and MAPK/p38 pathways control stress granule assembly in a hierarchical manner. Life Sci Alliance 2, e201800257

25. Buchan JR, Kolaitis RM, Taylor JP and Parker R (2013) Eukaryotic stress granules are cleared by autophagy and Cdc48/VCP function. Cell 153, 1461-1474

26. Wheeler JR, Matheny T, Jain S, Abrisch R and Parker R (2016) Distinct stages in stress granule assembly and disassembly. Elife 5, e18413

27. Markmiller S, Soltanieh S, Server KL et al (2018) Context-dependent and disease-specific diversity in protein interactions within stress granules. Cell 172, 590-604 e13

28. Song MS and Grabocka E (2020) Stress granules in cancer. Rev Physiol Biochem Pharmacol 14, 10.1007/112_2020_37

29. Marcelo A, Koppenol R, de Almeida LP, Matos CA and Nobrega C (2021) Stress granules, RNA-binding proteins and polyglutamine diseases: too much aggregation? Cell Death Dis 12, 592

30. Arimoto K, Fukuda H, Imajoh-Ohmi S, Saito H and Takekawa M (2008) Formation of stress granules inhibits apoptosis by suppressing stress-responsive MAPK pathways. Nat Cell Biol 10, 1324-1332

31. Thedieck K, Holzwarth B, Prentzell MT et al (2013) Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in cancer cells. Cell 154, 859-874

32. Moujaber O, Mahboubi H, Kodiha M et al (2017) Dissecting the molecular mechanisms that impair stress granule formation in aging cells. Biochim Biophys Acta Mol Cell Res 1864, 475-486

33. Omer A, Patel D, Lian XJ et al (2018) Stress granules counteract senescence by sequestration of PAI-1. EMBO Rep 19, e44722

34. Decker CJ and Parker R (2012) P-bodies and stress granules: possible roles in the control of translation and mRNA degradation. Cold Spring Harb Perspect Biol 4, a012286

35. Wilbertz JH, Voigt F, Horvathova I, Roth G, Zhan Y and Chao JA (2019) Single-molecule imaging of mRNA localization and regulation during the integrated stress response. Mol Cell 73, 946-958 e7

36. Ries RJ, Zaccara S, Klein P et al (2019) m(6)A enhances the phase separation potential of mRNA. Nature 571, 424-428

37. Fu Y and Zhuang X (2020) m^{6}A-binding YTHDF proteins promote stress granule formation. Nat Chem Biol 16, 955-963

38. He L, Li H, Wu A, Peng Y, Shu G and Yin G (2019) Functions of N6-methyladenosine and its role in cancer. Mol Cancer 18, 176

39. Khong A, Matheny T, Huynh TN, Babl V and Parker R (2022) Limited effects of m^{6}A modification on mRNA partitioning into stress granules. Nat Commun 13, 3735

40. Tourriere H, Chebli K, Zekri L et al (2003) The RasGAP-associated endoribonuclease G3BP assembles stress granules. J Cell Biol 160, 823-831

41. Kedersha N, Panas MD, Achorn CA et al (2016) G3BP-Caprin1-USP10 complexes mediate stress granule condensation and associate with 40S subunits. J Cell Biol 212, 845-860

42. Yang P, Mathieu C, Kolaitis RM et al (2020) G3BP1 is a tunable switch that triggers phase separation to assemble stress granules. Cell 181, 325-345 e28

43. Wang Y, Fu D, Chen Y et al (2018) G3BP1 promotes tumor progression and metastasis through IL-6/G3BP1/STAT3 signaling axis in renal cell carcinomas. Cell Death Dis 9, 501

44. Zhang LN, Zhao L, Yan XL and Huang YH (2019) Loss of G3BP1 suppresses proliferation, migration, and invasion of esophageal cancer cells via Wnt/beta-catenin and PI3K/AKT signaling pathways. J Cell Physiol 234, 20469-20484

45. Li Y, Wang J, Zhong S, Li J and Du W (2020) Overexpression of G3BP1 facilitates the progression of colon cancer by activating betacatenin signaling. Mol Med Rep

22, 4403-4411

46. Somasekharan SP, El-Naggar A, Leprivier G et al (2015) YB-1 regulates stress granule formation and tumor progression by translationally activating G3BP1. J Cell Biol 208, 913-929

47. Zheng H, Zhan Y, Zhang Y et al (2019) Elevated expression of G3BP1 associates with YB1 and p-AKT and predicts poor prognosis in nonsmall cell lung cancer patients after surgical resection. Cancer Med 8, 6894-6903

48. El-Naggar AM, Somasekharan SP, Wang Y et al (2019) Class I HDAC inhibitors enhance YB-1 acetylation and oxidative stress to block sarcoma metastasis. EMBO Rep 20, e48375

49. Park C, Choi S, Kim YE et al (2017) Stress granules contain Rbfox2 with cell cycle-related mRNAs. Sci Rep 7, 11211

50. Choi S, Sa M, Cho N, Kim KK and Park SH (2019) Rbfox2 dissociation from stress granules suppresses cancer progression. Exp Mol Med 51, 1-12

51. Reyes R, Alcalde J and Izquierdo JM (2009) Depletion of T-cell intracellular antigen proteins promotes cell proliferation. Genome Biol 10, R87

52. Heck MV, Azizov M, Stehning T, Walter M, Kedersha N and Auburger G (2014) Dysregulated expression of lipid storage and membrane dynamics factors in Tia1 knockout mouse nervous tissue. Neurogenetics 15, 135-144

53. Sanchez-Jimenez C, Ludena MD and Izquierdo JM (2015) T-cell intracellular antigens function as tumor suppressor genes. Cell Death Dis 6, e1669

54. Liu Y, Liu R, Yang F et al (2017) miR-19a promotes colorectal cancer proliferation and migration by targeting TIA1. Mol Cancer 16, 53

55. Arimoto-Matsuzaki K, Saito H and Takekawa M (2016) TIA1 oxidation inhibits stress granule assembly and sensitizes cells to stress-induced apoptosis. Nat Commun 7, 10252

56. Aldana-Masangkay GI and Sakamoto KM (2011) The role of HDAC6 in cancer. J Biomed Biotechnol 2011, 875824

57. Kwon S, Zhang Y and Matthias P (2007) The deacetylase HDAC6 is a novel critical component of stress granules involved in the stress response. Genes Dev 21, 3381-3394

58. Gal J, Chen J, Na DY, Tichacek L, Barnett KR and Zhu H (2019) The acetylation of lysine-376 of G3BP1 regulates RNA binding and stress granule dynamics. Mol Cell Biol 39, e00052-19

59. Zhang SL, Zhu HY, Zhou BY et al (2019) Histone deacetylase 6 is overexpressed and promotes tumor growth of colon cancer through regulation of the MAPK/ERK signal pathway. Onco Targets Ther 12, 2409-2419

60. Wippich F, Bodenmiller B, Trajkovska MG, Wanka S, Aebersold R and Pelkmans L (2013) Dual specificity kinase DYRK3 couples stress granule condensation/dissolution to mTORC1 signaling. Cell 152, 791-805

61. Mediani L, Antoniani F, Galli V et al (2021) Hsp90-mediated regulation of DYRK3 couples stress granule disassembly and growth via mTORC1 signaling. EMBO Rep 22, e51740

62. Rao R, Fiskus W, Yang Y et al (2008) HDAC6 inhibition enhances 17-AAG–mediated abrogation of hsp90 chaperone function in human leukemia cells. Blood 112, 1886-1893

63. Ory B, Baud'huin M, Verrecchia F et al (2016) Blocking HSP90 addiction inhibits tumor cell proliferation, metastasis development, and synergistically acts with zoledronic acid to delay osteosarcoma progression. Clin Cancer Res 22, 2520-2533

64. Song KH, Oh SJ, Kim S et al (2020) HSP90A inhibition promotes anti-tumor immunity by reversing multi-modal resistance and stem-like property of immune-refractory tumors. Nat Commun 11, 562

65. Yin L, Yang Y, Zhu W et al (2021) Heat shock protein 90 triggers multi-drug resistance of ovarian cancer via AKT/GSK3beta/beta-catenin signaling. Front Oncol 11, 620907

66. Simanshu DK, Nissley DV and McCormick F (2017) RAS proteins and their regulators in human disease. Cell 170, 17-33

67. Redding A, Aplin AE and Grabocka E (2022) RAS-mediated tumor stress adaptation and the targeting opportunities it presents. Dis Model Mech 15, dmm049280

68. Grabocka E and Bar-Sagi D (2016) Mutant KRAS enhances tumor cell fitness by upregulating stress granules. Cell 167, 1803-1813 e12

69. Fournier MJ, Gareau C and Mazroui R (2010) The chemotherapeutic agent bortezomib induces the formation of stress granules. Cancer Cell Int 10, 12

70. Kaehler C, Isensee J, Hucho T, Lehrach H and Krobitsch S (2014) 5-Fluorouracil affects assembly of stress granules based on RNA incorporation. Nucleic Acids Res 42, 6436-6447

71. Park YJ, Choi DW, Cho SW, Han J, Yang S and Choi CY (2020) Stress granule formation attenuates RACK1-mediated apoptotic cell death induced by morusin. Int J Mol Sci 21, 5360

72. Adjibade P, Simoneau B, Ledoux N et al (2020) Treatment of cancer cells with Lapatinib negatively regulates general translation and induces stress granules formation. PLoS One 15, e0231894

73. Shi Q, Zhu Y, Ma J et al (2019) Prostate cancer-associated SPOP mutations enhance cancer cell survival and docetaxel resistance by upregulating Caprin1-dependent stress granule assembly. Mol Cancer 18, 170

74. Timalsina S, Arimoto-Matsuzaki K, Kitamura M et al (2018) Chemical compounds that suppress hypoxia-induced stress granule formation enhance cancer drug sensitivity of human cervical cancer HeLa cells. J Biochem 164, 381-391

75. Attwood KM, Robichaud A, Westhaver LP et al (2020) Raloxifene prevents stress granule dissolution, impairs translational control and promotes cell death during hypoxia in glioblastoma cells. Cell Death Dis 11, 989

76. Zhao J, Fu X, Chen H et al (2021) G3BP1 interacts with YWHAZ to regulate chemoresistance and predict adjuvant chemotherapy benefit in gastric cancer. Br J Cancer 124, 425-436

77. Cho E, Than TT, Kim SH et al (2019) G3BP1 depletion increases radiosensitisation by inducing oxidative stress in response to DNA damage. Anticancer Res 39, 6087-6095

78. Weipoltshammer K, Schofer C, Almeder M et al (1999) Intranuclear anchoring of repetitive DNA sequences: centromeres, telomeres, and ribosomal DNA. J Cell Biol 147, 1409-1418

79. Gilks N, Kedersha N, Ayodele M et al (2004) Stress granule assembly is mediated by prion-like aggregation of TIA-1. Mol Biol Cell 15, 5383-5398

80. Dewey CM, Cenik B, Sephton CF et al (2011) TDP-43 is directed to stress granules by sorbitol, a novel physiological osmotic and oxidative stressor. Mol Cell Biol 31, 1098-1108

81. Do TQ, Gaudreau-Lapierre A, Palii CG et al (2020) A nuclear stress pathway that parallels cytoplasmic stress granule formation. iScience 23, 101664

82. Fu X, Gao X, Ge L et al (2016) Malonate induces the assembly of cytoplasmic stress granules. FEBS Lett 590, 22-33

83. Stoecklin G, Stubbs T, Kedersha N et al (2004) MK2-induced tristetraprolin:14-3-3 complexes prevent stress granule association and ARE-mRNA decay. EMBO J 23, 1313-1324

84. Fujimura K, Kano F and Murata M (2008) Identification of PCBP2, a facilitator of IRES-mediated translation, as a novel constituent of stress granules and processing bodies. RNA 14, 425-431

85. Mazroui R, Di Marco S, Kaufman RJ and Gallouzi IE (2007) Inhibition of the ubiquitin-proteasome system induces stress granule formation. Mol Biol Cell 18, 2603-2618

86. Seguin SJ, Morelli FF, Vinet J et al (2014) Inhibition of autophagy, lysosome and VCP function impairs stress granule assembly. Cell Death Differ 21, 1838-1851

87. Thomas MG, Martinez Tosar LJ, Loschi M et al (2005) Staufen recruitment into stress granules does not affect early mRNA transport in oligodendrocytes. Mol Biol Cell 16, 405-420

88. Buchan JR, Yoon JH and Parker R (2011) Stress-specific composition, assembly and kinetics of stress granules in Saccharomyces cerevisiae. J Cell Sci 124, 228-239

89. Herman AB, Silva Afonso M, Kelemen SE et al (2019) Regulation of stress granule formation by inflammation, vascular injury, and atherosclerosis. Arterioscler Thromb Vasc Biol 39, 2014-2027

90. Slaine PD, Kleer M, Smith NK, Khaperskyy DA and McCormick C (2017) Stress granule-inducing eukaryotic translation initiation factor 4A inhibitors block influenza a virus replication. Viruses 9, 388

91. Henderson KA, Kobylewski SE, Yamada KE and Eckhert CD (2015) Boric acid induces cytoplasmic stress granule formation, eIF2alpha phosphorylation, and ATF4 in prostate DU-145 cells. Biometals 28, 133-141

92. Moeller BJ, Cao Y, Li CY and Dewhirst MW (2004) Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer Cell 5, 429-441

93. Ying S and Khaperskyy DA (2020) UV damage induces G3BP1-dependent stress granule formation that is not driven by mTOR inhibition-mediated translation arrest. J Cell Sci 133, jcs248310

94. Deng C, Ji X, Rainey C, Zhang J and Lu W (2020) Integrating machine learning with human knowledge. iScience 23, 101656

95. Adjibade P, St-Sauveur VG, Quevillon Huberdeau M et al (2015) Sorafenib, a multikinase inhibitor, induces formation of stress granules in hepatocarcinoma cells. Oncotarget 6, 43927-43943

96. Szaflarski W, Fay MM, Kedersha N, Zabel M, Anderson P and Ivanov P (2016) Vinca alkaloid drugs promote stress-induced translational repression and stress granule formation. Oncotarget 7, 30307-30322

97. Pietras P, Aulas A, Fay MM et al (2022) Translation inhibition and suppression of stress granules formation by cisplatin. Biomed Pharmacother 145, 112382

98. Vilas-Boas Fde A, da Silva AM, de Sousa LP et al (2016) Impairment of stress granule assembly via inhibition of the eIF2alpha phosphorylation sensitizes glioma cells to chemotherapeutic agents. J Neurooncol 127, 253-260

99. Gareau C, Fournier MJ, Filion C et al (2011) p21(WAF1/CIP1) upregulation through the stress granule-associated protein CUGBP1 confers resistance to bortezomib-mediated apoptosis. PLoS One 6, e20254