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ABSTRACT

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.

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.

1. 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 (11, 12) (Fig. 1). 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 (15) (Fig.1). 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 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.

2. 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.

2.1 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 (7, 29) (Fig. 2).

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 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).

2.2 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^6A), the most prevalent internal modification on mRNA, can regulate mRNA stability (38). It has been demonstrated that mRNAs containing multiple, but not single, m^6A 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^6A nucleotides is correlated with SGs enrichment regardless of transcript length (36). Likewise, m^6A-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^6A modification might modulate SGs targeting of RNAs. However, a recent study has found that m^6A modifications have limited effects on mRNA recruited into SGs (39). Thus, the relationship of m^6A modification with SGs targeting remains to be elucidated.

3. 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.

3.1 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.

3.2 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 tumorigenesis (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.

4. 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 (Table 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 eIf2α 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 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.

5. 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.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

362 **FIGURE LEGENDS**

363 **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 phosphorylation of eIF2α	HeLa (0.5 mM for 30 min), DU145 and COS-7 (0.5 mM for 30 min	(78, 79)
Sorbitol	Oxidative stress Osmotic 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	Disrupt eIF4F complex	U2OS (1 mM for 2 h)	(18)
Malonate	Mitochondrial inhibitor (Oxidative stress, Energy depletion)	Inducing 4EBP1 hypophosphorylation	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 inhibitor (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 1.5h)	(5)
Dithiothreitol (DTT)	ER stress	Inducing eIF2α phosphorylation	HeLa (1 mM for 1 h)	(84)
Lactacystin	Proteasome inhibitor	Inducing eIF2α phosphorylation(GCN2)	HeLa (10 μM for 4 h)	(85)
MG132	Proteasome inhibitor	Proteasome inhibitor	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 inhibitor	Decreasing polysomes disruption of the mitochondrial function	BY4741 (0.5 %(v/v) for 30 min)	(88)

Clotrimazole	Causing energy starvation	Inhibiting Hexokinase II	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	Natural product	Inducing eIF2α phosphorylation(PKR)	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	Promoting eIF4A inactivation	HeLa (50 μM for 0.5 h), DLD1 (50 μM for 1 h)	(72, 77)
Rocaglamide A	Natural product	Inhibiting eIF4A	U2OS (1 μM for 1 h)	(81)
UV irradiation	DNA damage	Inducing eIF2α phosphorylation (GCN2)	U2OS (10 or 20 mJ/cm for 2 h)	(92, 93)
Heat shock	Protein denaturation	Inducing phosphorylation of eIF2α(GCN2)	HeLa (43.5 °C for 45 min)	(86)
Cold shock	Low temperature stress	Inducing eIF2α phosphorylation (PERK)	COS7 (10 ºC for 10 h)	(2)
Bortezomib	Proteasome inhibitor	Inducing eIF2α phosphorylation(HRI)	HeLa (1 μM for 3 h), U2OS (25 μM for 4 h)	(69, 94)
Sorafenib	Proteasome inhibitor	Inducing eIF2α phosphorylation(PERK)	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 drug	Inducing eIF2α phosphorylation and 4EBP1 dephosphorylation	U2OS (150 μM for 1 h)	(96, 97)
Vinblastine	Microtubule disruption drug	Inducing eIF2α phosphorylation and 4EBP1 dephosphorylation	U2OS (300 μM for 1 h)	(96)
Vincristine	Microtubule disruption drug	Inducing eIF2α phosphorylation and 4EBP1 dephosphorylation	U2OS (750 μM for 1 h)	(96)
Oxaliplatin	DNA damage drug	Inducing eIF2α phosphorylation(PERK)	U2OS (600 μM, 2 mM for 4 h)	(97)

Cisplatin	DNA damage drug	Inducing eIF2α phosphorylation	Glioma C6, U87MG (5 mM for 2 h), U2OS (250 μM for 4 h)	(97, 98)
Carboplatin	DNA damage drug	Inducing eIF2α phosphorylation	U2OS (10 mM for 4 h)	(97)
Fluorouracil (5-FU)	Incorporation into RNA	Inducing eIF2α phosphorylation(PKR)	HeLa (0.1 mM for 72 h)	(70)
6-Thioguanine	Incorporation into RNA	Inducing eIF2α phosphorylation(PKR)	HeLa (10 μM for 72 h)	(70)
5-Azacytidine	Incorporation into RNA	Inducing eIF2α phosphorylation(PKR)	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(PERK)	T47D (20 μM for 2h)	(72)

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367 **Table 2. SGs-mediated chemotherapy resistance**

Chemotherapeutic reagent	Cancer type	Mechanism of drug resistance via SGs formation	References
Bortezomib	myelomas and other hematological tumors	Sequestration of *p21*(cyclin-dependent kinase inhibitor) mRNA into SGs	(69, 99)
5-fluorouracil (5-FU)	Proteasome inhibitor	Sequestration of RACK1 (pro-apoptotic protein) within into SGs	(70)
Morusin	Inflammatory pulmonary diseases, diabetes, neurocognitive diseases	Sequestration of RACK1 (pro-apoptotic protein) into SGs	(71)
Docetaxel	Prostate cancer	SPOP mutation Caprin1 overexpression	(73)
Cisplatin	Glioma	*G3BP1* overexpression (*G3BP1* mRNA↑)	(74)
Paclitaxel	Glioma	*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)

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Figure 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.

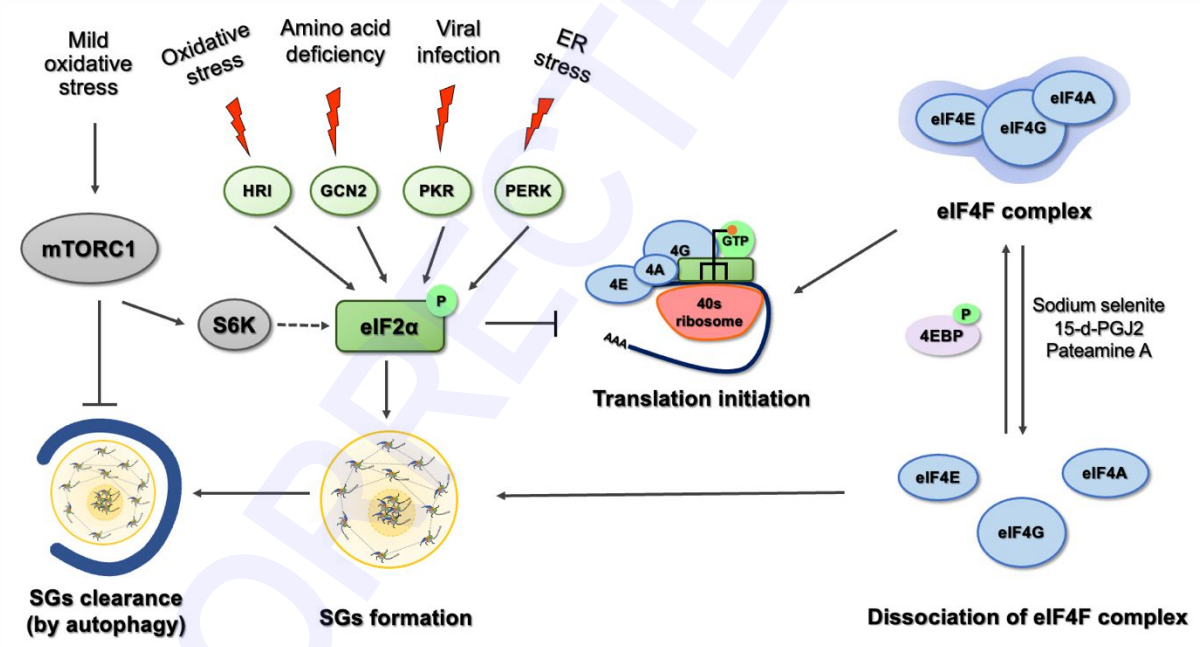
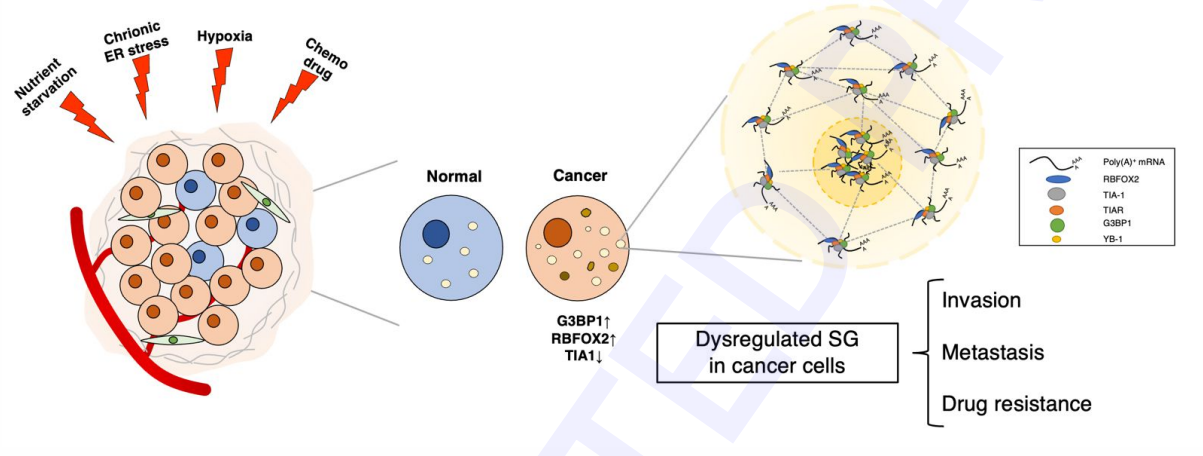


Figure 2. An overview of the effect of tumor-associated stress and SGs in cancer cells during tumor progression.

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.



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