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Review Article

Understanding the roles of stress granule during chemotherapy for patients with malignant tumors

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Abstract: The assembly of stress granules (SGs) is a conserved mechanism to regulate protein synthesis under cell stress, where the translation of global protein is silenced and selective protein synthesis for survival maintains. SG formation confers survival advantages and chemotherapeutic resistance to malignant cells. Targeting SG assembly may represent a potential treatment strategy to overcome the primary and acquired chemotherapeutic resistance and enhance curative effect. We conduct a comprehensive review of the published literatures focusing on the drugs that potentially induce SGs and the related mechanism, retrospect the relationship between SGs and drug resistance related proteins, illuminate the regulated pathways and potential targets for SG assembly, and discuss future directions of overcoming the resistance to chemotherapy.

Keywords: Stress granule, G3BP1, chemotherapy, chemoresistance, mTOR signaling

Introduction

Eukaryotic cells are formed of many compartments or organelles to separate or concentrate biological progress. Taking protein translation as an example, translation initiates in the cytosol for secretory or integral membrane proteins, ribosomes containing mRNAs are recruited to the endoplasmic reticulum (ER) membrane. Once the translation are complete, membrane proteins will be shifted and anchored within the phospholipid bilayer, while secretory proteins may undergo folding and modifications in the ER and be released by the chaperones and packaged by Golgi apparatus for vesicle trafficking [1-3]. ER and Golgi apparatus are membranous organelle and the ribosome is non-membranous. The membranous or non-membranous organelles are playing important roles in protein translation, whereas non-membranous compartments can't be neglected in the suspended translation process especially for cells exposed to the stress.

Cancer cells are exposed to adverse conditions in the tumor microenvironment such as nutrient deprivation, hypoxia, DNA damage, oxidative stress, inflammation, reduced PH, immune attack and radical or chemical treatment, which compels malignant cells to make adaptive changes to ensure survival [4, 5]. When confronted with stress, one highly conserved mechanism is reducing global protein synthesis and maintaining selective protein synthesis that of the essence for cell survival [6-8]. Stress granules (SGs), one kind of non-membranous compartment in the cytoplasm, are assemblies of untranslating messenger ribonucleoproteins (mRNPs) that form from mRNAs stalled in translation initiation [9]. Since no membrane-like structure, interactions between protein-and-protein as well as protein-and-RNA are significant. Besides mRNPs, many other components are also involved in the assembly of SGs including RNA-binding proteins (such as G3BP1 [10-12], IMP1 [10], TIA1 [13], *et al.*), translation initiation factors (such as eIF3 [14], eIF4A/B [14, 15], eIF4E [16], eIF4G [14] , *et al.*), poly-A-binding protein (such as Pab1 in saccharomyces [17], PABP1 [18], *et al.*) and ribosomal subunits (such as 40S subunits [11, 12]). In most cases, the formation of SGs is requiring the phosphory-

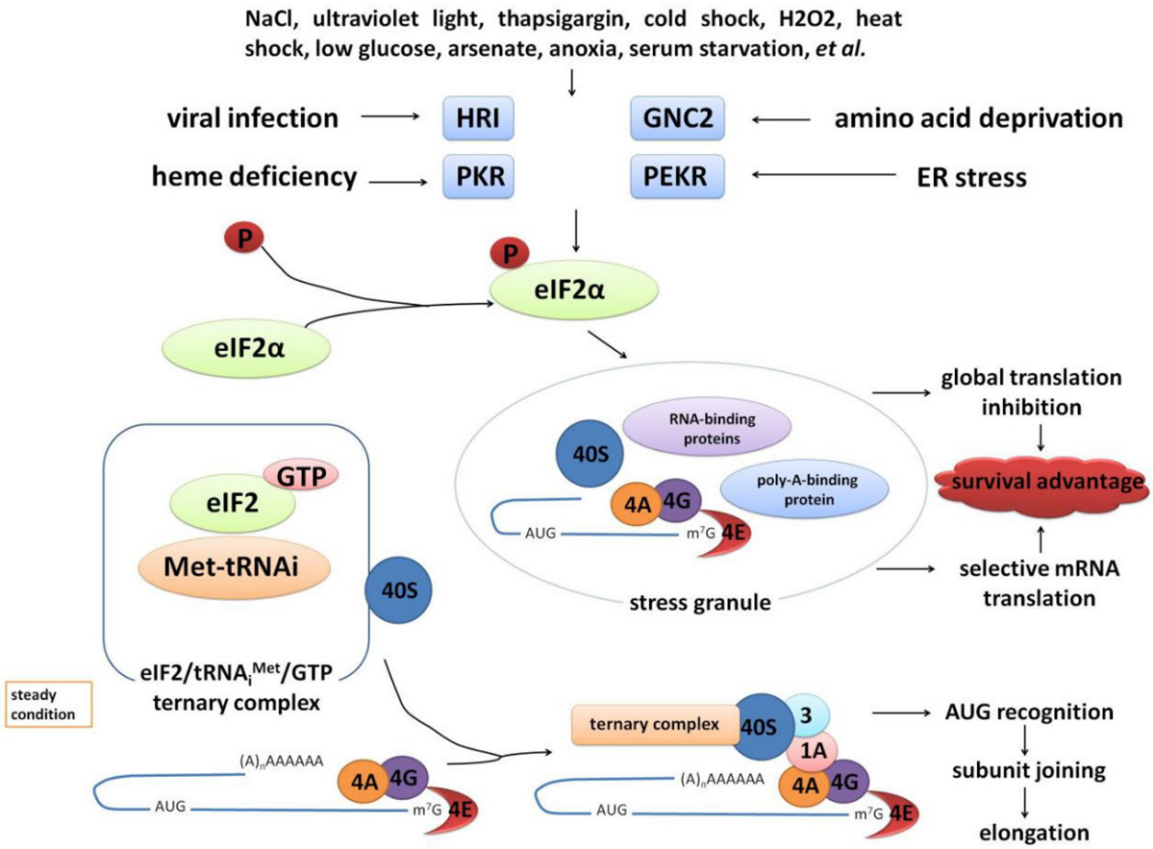

Figure 1. The assembly of stress granules in the phosphorylation of eIF2α dependent manner. Under steady-state conditions, eIF2/$tRNA_i^{Met}$/GTP ternary complex can bind initiator $tRNA_i^{Met}$ to the 40S ribosomal subunit in a GTP-dependent manner. Adverse conditions activate the eIF2α kinases (HRI, PKR, PERK and GCN2) and lead to phosphorylation of eIF2α, which damage the ternary complex and impair translational initiation, following the formation of SGs. SGs are assemblies of untranslating messenger ribonucleoproteins that form from mRNAs stalled in translation initiation, also containing RNA-binding proteins, translation initiation factors, poly-A-binding protein and 40S ribosomal subunits.

lation of the translation initiation factor eIF2α [19]. Under steady-state conditions, eIF2/$tRNA_i^{Met}$/GTP ternary complex can bind initiator $tRNA_i^{Met}$ to the 40S ribosomal subunit in a GTP-dependent manner. Adverse conditions activate the eIF2α kinases and lead to phosphorylation of eIF2α, which damage the ternary complex and impair translational initiation, following the formation of SGs [5]. Phosphorylation of eIF2α on serine 51 can be activated by a family of four kinases, heme-regulated inhibitor (HRI), protein kinase R (PKR), PKR-like endoplasmic reticulum kinase, (PERK) and general control non-depressible 2 (GCN2) [20-22]. All four kinases have catalytic domain, and are supposed to be activated by homodimerization and autophosphorylation [23]. Each kinase can be activated by a specific stress. HRI is activated during heme deficiency [24]; PKR is activated by viral infection [25, 26]; PERK is activated during ER stress [27]; GCN2 is activated under amino acid deprivation [28]. Different stimulus can cause different intensity of eIF2α phosphorylation. NaCl, ultraviolet light and thapsigargin cause strong eIF2α phosphorylation; cold shock, H_2O_2, heat shock, low glucose, arsenate, and histidinol cause moderate phosphorylation; polyinosinic polycytidylic acid, anoxia, and serum starvation cause mild phosphorylation [21] (**Figure 1**). In some cases such as response to mammalian orthoreovirus, the formation of SGs is eIF2α independent [29]. Besides, in the brain ischemia-reperfusion process, SG formation is correlated with the decreased expression of the cap-binding protein eIF4E and the eIF4B [30]. Selenite can induce SGs formation via eIF4E-binding protein 1 (4EBP1)-mediated inhibition of translation initiation [31].

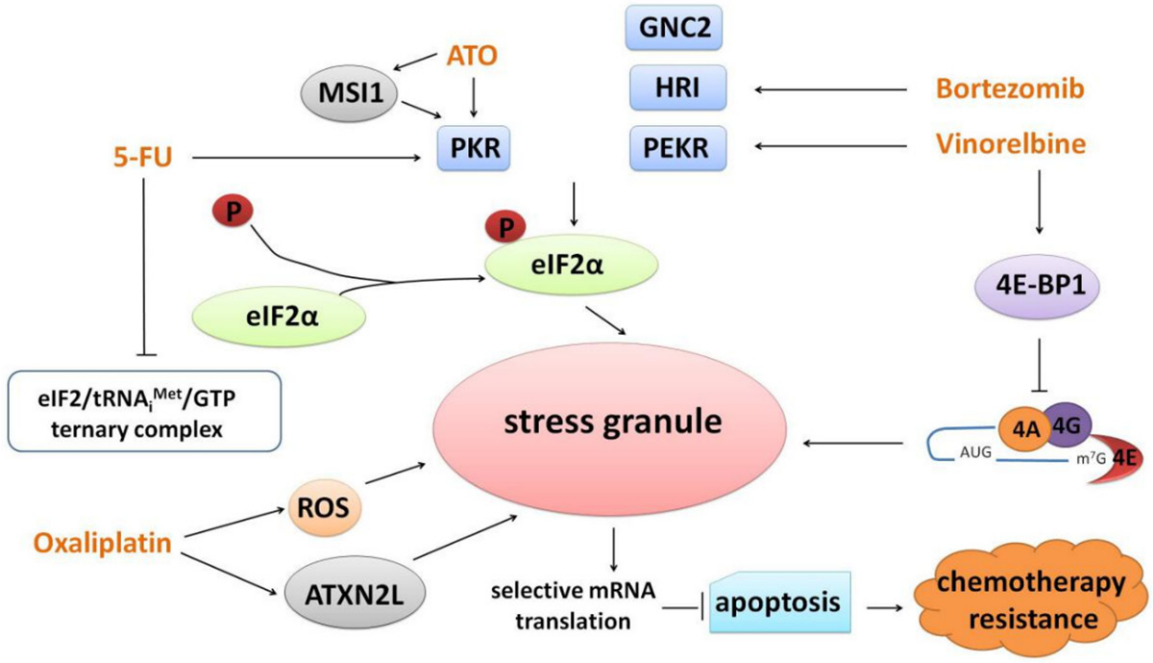

Figure 2. Stress granules can be induced by chemotherapy drugs. Platinum induce reactive oxygen species and lead to SGs assembly. PKR protein can be activated by 5-Fluorouracil, inducing phosphorylation of eIF2α and cell death by apoptosis. Arsenic trioxide, vinorelbine and bortezomib can cause phosphorylation of eIF2α by activating PKR, PERK and HRI respectively.

SGs are non-membrane bound cytoplasmic entities, and "Core first" model and "liquid-liquid phase separations (LLPS) first" model have been established to explain the assembly of SGs. "Core first" model, the traditional concept, is a process starting to untranslating mRNAs with bound SG-nucleating proteins (such as TIA1, G3BP1, TTP, FMRP, CAPRIN1 *et al.*) oligomerize into stable cores, and the outer shell forms later [32, 33]. The other concept of SGs formation is called "LLPS first" model, which thinks SG formation before the core concentrate. In this view, the increasing pool of untranslated mRNAs bound by proteins containing intrinsically disordered protein regions (IDRs), firstly lead to the formation of a LLPS based on IDR-IDR interactions. And the cores assemble following with the increased local concentration of its components [34].

SGs assembly is a conserved cellular response to minimize stress-related damage and promote cell survival. The aberrant assembly or disassembly of SGs is believed to participate in neurodegenerative disorders, ischemia-reperfusion process, virus infections and cancer initiation or development. Various chemotherapy drugs can modulate SG formation and dynamics, in the meantime, SGs, as the signaling center, are promising targets for cancer treatment. In this review, we summarize the clinical drugs for inducing SGs assembly and their related mechanism, as well as the potential roles of SGs in cancer treatment, in the interest of providing new perspectives for overcoming chemotherapy resistance.

Stress granules can be induced by chemotherapy drugs

Cancer treatment is now multidisciplinary. In theory, it is potential to cause SGs assembly by any chemotherapeutic drug that influence the translation process or targeting translation element in cells (**Figure 2**).

Platinum and platinum-containing drugs

Platinum, the most effective agent for nearly all types of malignant tumor, has been linked its effect to the ability of influencing the purine bases on the DNA, interfering with DNA repair mechanisms, causing DNA damage, blocking cell division and inducing apoptosis in cancer cells [35]. Not only damaging DNA directly, plat-

inum also induce reactive oxygen species (ROS) in cells and cause oxidative stress [36, 37]. Oxidative stress is one of the conditions that induce SG assembly. ROS, such as H_2O_2, is routinely used as inducer for oxidative stress or SGs [33, 38]. Ataxin-2-like (ATXN2L) is a regulator of SGs and processing bodies. ATXN2L overexpression induces the formation of SGs, while the reduced ATXN2L affects the size and number of SGs [39]. ATXN2L is found upregulated in gastric cancer tissue and indicated adverse prognosis for overall survival and recurrence. Oxaliplatin is proved to promote ATXN2L expression and SG assembly. The oxaliplatin-resistant cell lines present with elevated ATXN2L levels, while silencing ATXN2L can reverse the oxaliplatin resistance by increasing ROS production and apoptosis [40]. In contrast to oxaliplatin, cisplatin fails to induce immunogenic tumor cell death, which may attribute to its incapacity to translocate calreticulin from the lumen of the ER to the cell surface [41]. It is indicated that cisplatin is unable to activate the PERK-dependent phosphorylation of eIF2α in U2OS cells (osteosarcoma cell), and fails to stimulate the formation of SGs. When combined cisplatin and thapsigargin (an inhibitor of the sarco/ER Ca2+-ATPase, does not stimulate calreticulin exposure), phosphorylation of eIF2α and SGs can be detected [42]. Certainly, the ability of inducing SGs depends on cell types, cisplatin may lead to SGs assembly in malignant glioma cells, and impairment of SG assembly may sensitize cells to cisplatin [43].

In fact, it is difficult to delimitate the advantageous or disadvantageous roles for SGs in cancer treatment. After cisplatin treatment, more dead cells were found in G3bp1-knockdown cells (less SGs formation) compared with controls, accompanied by increases in cleaved/active caspase-3. SGs are formed to protect proximal tubular cells under adverse condition [44]. The combination of cisplatin and thapsigargin may promote phosphorylation of eIF2α and SGs formation, enhance immunogenic cell death [42], which drives efficient antitumor effects [45]. The above studies show that the formation of SGs may play positive roles in cancer treatment, for protecting proximal tubular cells or increasing the antitumor effects. However, some studies indicate that oxidative stress and SGs formation facilitate cancer cells to acquire chemoresistance, which is negative for cancer treatment [40, 43].

5-Fluorouracil (5-FU)

The mechanism of cytotoxicity of 5-FU has been attributed to the inhibition of the nucleotide synthetic enzyme thymidylate synthase (TS), and to the misincorporation of 5-FU metabolites into DNA and RNA. When 5-FU metabolites incorporate into RNA, the processing and maturation of rRNA, tRNA and snRNA are all influenced [46, 47]. Phosphorylation of eIF2α may damage eIF2/$tRNA_i^{Met}$/GTP ternary complex and impair translational initiation, leading to the formation of SGs [5]. It is reported that PKR protein can be activated by 5-FU, inducing phosphorylation of eIF2α and cell death by apoptosis [48]. Clinically, PKR and its regulator, the non-coding RNA pre-miR-886 (nc886), are established to evaluate the patients' prognosis and response to 5-FU-based chemotherapy. Higher levels of nc886 predicts better response to treatment, and the cases lacking PKR location in the nucleolus show a positive relationship with 5-FU-based chemotherapy [49]. Interesting, PKR has been identified as the key target for 5-FU promoting apoptosis; however, the active PKR also leads to phosphorylation of eIF2α and induce SGs assembly, thereby assisting tumor cells overcome 5-FU-induced cytotoxicity and leading to chemoresistance [50]. 5-FU-induced SGs contain RACK1, a promoter for cell apoptosis, and the sequestration of RACK1 to SGs may suppress the stress-responsive MAPK pathways therefore inhibiting apoptotic cascades and inducing resistance to chemotherapy [50-52]. It seems to be contradictory that increased expression of PKR is associated with better clinical outcome for lymph node negative rectal cancer patients who have received post-operative chemoradiation based on 5-FU [53]. We recommend readers to keep a watchful eye on tumor load, the study of Ortega-García MB *et al.* intakes colon metastatic cancer patients with unresectable lung or liver metastases [49], while Kwon HC and his colleagues observe lymph node negative rectal cancer patients [53]. Despite multiple studies of PKR, the exact role in cancer biology and integrated stress response (ISR) remains controversial. On the one hand, PKR can induce apoptosis via caspase-8 and caspase-9 pathway [54]; on the other hand, PKR may lead to phosphorylation of eIF2α and promote SGs assembly, leading to chemoresistance.

Arsenic trioxide (ATO) and sodium arsenite (SA)

Low-dose ATO, an agent that induces oxidative stress and interferes with protein translation, is always combined with all-trans-retinoic acid (ATRA) to treat acute promyelocytic leukemia [55], while large-dose ATO or SA is the most common reagent for inducing SGs [21]. *In vitro*, the ATO concentration for inducing cell differentiation is always less than 1 uM [56, 57], for studying cell apoptosis is between 1 and 5 uM [57-59], for initiating SGs formation is from 100 to 500 uM (about 1 hour) [11, 16, 60]. The specific concentration and time differs from each experiment, however, the incremental concentration seems to enlighten us that SGs formation is a kind of rapid-response strategy to cope with the lethal attack. When treated with ATO, the SGs formation is PKR and phosphorylation of eIF2α dependent [61]. One of antitumor methods for ATO is the induction of apoptosis, and pretreatment of ER stress inducer may enhance ATO efficiency; activation of p53 can be observed in this process [59, 62]. ER stress can be induced by ATO, a mitochondrial toxin, and triggers tumor cells apoptosis involving interplay of ER and mitochondria [63]. However, the lethal stress also urges cells form SGs and strives for ability to survive, leading to resistance to chemotherapy. The overexpression of Musashi-1 (MSI1) can be detected in tumor tissues compared with adjacent normal tissues, and correlated with poor overall survival [64, 65]. MSI1 activates PKR/p-eIF2α/SGs axis in response to cytotoxic stress from ATO treatment, and reduces ATO-induced apoptosis in glioblastoma multiforme cells [66]. ATO functions as effective anti-tumor drug for triggering cell apoptosis; however, there are various mechanisms for malignant cells to response to ATO and evade apoptosis, and inducing SGs formation may be a potential synergia for overcome ATO resistance. For example, cells become resistant to SA after repeated SA treatment, which changes in SG biology and the pool of secreted factor, increasing survival response and resulting in chemo-resistance [67].

Phytogenic anticarcinogen: vinca alkaloids and paclitaxel

Microtubule-targeting agents (MTAs) such as paclitaxel and vinca alkaloids are one of the most important chemotherapy drugs available to combat cancer. MTAs influence mitotic spindle formation by interfering microtubule dynamics during mitosis, leading to cell cycle arrest, apoptosis, vascular disrupting to combat cancer [68, 69]. It is reported that microtubule dynamic instability favors the assembly of SGs [70]. SGs are induced by SA, vinca alkaloids, the microtubule-depolymerizing drug, may abolish arsenate-induced formation of SGs, while the microtubule-stabilizing drug paclitaxel has the opposite effects [71]. Interestingly, vinca alkaloids (vinorelbine) are the potent inducers of SGs, which is dose- and time-dependent. Vinorelbine promote SG formation in a phospho-eIF2α dependent manner via activation of PERK kinase; and it also promotes dephosphorylation of 4E-BP1 and disrupts eIF4F complex formation. Interestingly, depletion of PERK and/or 4E-BP1 can sensitize cell for vinorelbine and increase cell apoptosis [72].

Treated cells with paclitaxel can induce SGs formation, tubulin is not found in SGs [72]. The specific mechanism for paclitaxel inducing SGs is not known. But to be sure, translation is significantly inhibited during paclitaxel-induced apoptosis in cancer cells, which is involved in elongation factor eEF2, rather than phosphorylation of eIF2α, eIF4G, eIF4E and 4E-BP1, although the decrease of eIF4G, eIF4E and 4E-BP1 expression levels can be detected [73].

Bortezomib

Bortezomib, a peptide boronate inhibitor of the 26S proteasome, is applied in the clinical treatment and observed to improve the prognosis of multiple myeloma and mantle cell lymphoma [74, 75]. Bortezomib is proved to result in cell apoptosis, and solid tumor cells are largely refractory to bortezomib [76]. There is no certain mechanism why solid tumor is not sensitive to bortezomib, and SGs formation probably one of the potential explanations. Bortezomib induces the assembly of SGs in cancer cells involving the phosphorylation of eIF2α via HRI activation, causing a reduction of global translation; the disassembly of SGs and the associated translation recovery doesn't need dephosphorylation of eIF2α [77]. It is reported that inhibition of eIF2α and impairment of SG assembly by knocking down G3BP1 can sensitize gliomas cells to bortezomib [43, 78]. Notably, knocking down G3BP1 may significant increase in the apoptotic response to bortezo-

mib with increased expression of caspase-3 [78]. Moreover, Bortezomib induces the localization of CUGBP1-p21mRNA in SGs, while p21 upregulation can promote cancer cell resistance to bortezomib [79]. Given that targeting SGs may enhance the sensitivity to bortezomib, the combination of bortezomib and small molecules seems to be promising method to overcome resistance of bortezomib in solid tumor treatment. It is found psammaplysin F, a kind of marine sponge-derived metabolite, can decrease the number of SGs with the induction of ATO, and enhance the efficacy of bortezomib in HeLa and MCF7MDR cells, which represent a useful strategy to improving drug efficacy [80].

Stress granules contribute to chemotherapy resistance

Stress granules and ABC transporters

The expression of drug resistance-related proteins limits the efficacy of current chemotherapeutic agents. When exposed to stress, eukaryotic cells may selectively shut down the translation of constitutively expressed genes, and simultaneously maintain or enhance the translation of specific stress-induced transcripts [4]. Overexpression of P-glycoprotein, encoded by multidrug resistance 1 (*MDR1*), is often responsible for multidrug resistance and chemotherapy failure in cancer treatment [81]. It is observed that *MDR1* mRNAs do not colocalize with TIA-1 (SG-nucleating protein) and are not sequestered into SGs on arsenite treatment. Interesting, *MDR1* and other ER-associated transcripts retain their polyribosomes, tether the transcripts to the ER. On withdrawal of stress, the translational status of *MDR1* mRNA recovers more quickly than that of other mRNAs such as *ACTB* and *ATF4* (normally sequestered in SGs [82]), and endows survival priority to tumor cells and induce resistance to chemotheraputic agents [83, 84].

Protein kinase C (PKC), a family of serine/threonine kinases, mediates the induction of P-glycoprotein to increase drug resistance in multiple cancers [85]. It is reported that PKCα interacts with G3BP2 and localizes to SGs; downregulation of PKCα delays induction of eIF2α phosphorylation and SG formation [86]. More and deeper studies need to be done to detect the relationship and regulation mechanism of other drug resistance related proteins (such as MRP, BCRP and LRP) and SGs assembly and disassembly in the future.

Stress granules and cell stemness

Cancer stem cells (CSCs), a small amount of cells conferring to the capacity to self-renew, are supposed to partially responsible for chemotherapy resistance, and cancer cells that undergo epithelial-to-mesenchymal transition (EMT) have been shown to acquire stemness and undergo metabolic changes [87, 88]. It is reported that knockdown of G3BP1 inhibit the EMT process with the alteration of Cadherins, Vimentin, Snail, Slug, c-Myc, and cyclin D1 [89]. G3BP2 also regulates expression of Oct-4, Nanog and SART3 [90], which are the potential molecular markers for further characterization of CSCs [87]. Meanwhile, *Musashi-1*, a stemness gene as well as colon and neuronal stem cell marker, triggers the formation of anti-apoptotic SGs with 5-FU and Musashi-1 SGs enhance the chemoresistance of colorectal cancer in turn [91]. In fact, Musashi-1 is proved to be associated with progression and poor prognosis of many kinds of cancers [92, 93], and is thought as a novel target in cancer treatment due to its ability to maintain stemness and promote SGs formation [66, 94, 95].

Stress granules and apoptosis

The therapeutic effects of chemotherapy drugs largely rely on the trigger of a cascade of apoptosis process, and therefore, the assembly of SGs can partially offset the apoptotic functions of chemotherapy drugs and result in chemotherapy resistance. For example, the SG assembly is reduced by bortezomib after knockdown of G3BP1 with increased Caspase-3 activation, enhancing the effects of bortezomib [78]. Inhibiting phosphorylation of eIF2α also promotes apoptosis by reducing SGs assembly [96]. In fact, SGs are the crossroads of apoptosis process and stress response, and regulate type I and type II stress by sequestering RACK1, relevant to hypoxia-induced chemoresistance [52].

Stress granules and autophagy

Autophagy is a double sword in cancer treatment, no matter protective autophagy inhibition or autophagy overactivation may introduce cell death pathway in addition to apoptosis and

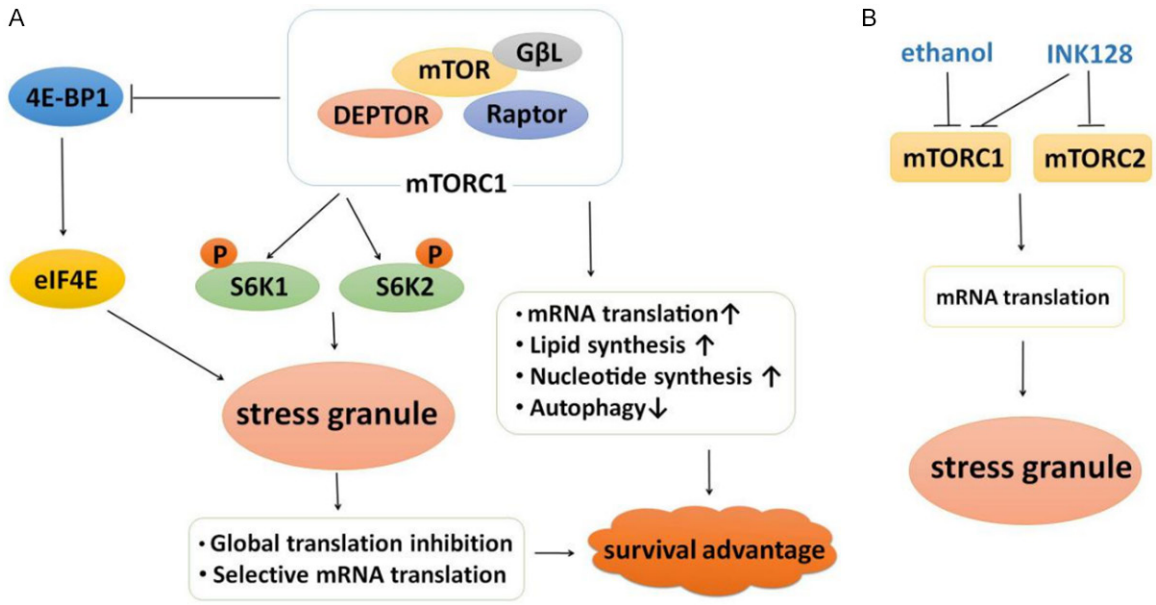

Figure 3. The different roles of mTOR signaling in stress granules assembly. A. The activation of mTOR-S6 kinase pathway facilitates malignant progression of malignant tumor, and also promotes SGs assembly. The mTOR-S6 kinase pathway can promote SG assembly in response to mild oxidative stress by eIF2α phosphorylation, and mTOR/4EBP1/eIF4E axis enhances the ability of SGs assembly. B. mTORC1 is a main activator of translation, and thus translation arrest through mTORC1 inhibition may has potential to induce SGs assembly.

seem to be effective in combating chemoresistance and radioresistance in malignant tumors [97]. It is validated autophagosomes are associated with clearance of SGs and help cells to survive the stress stimulus. Treated with SA or MG132, Syk is recruited in SGs by Grb7, and the recruitment requires the phosphorylation of Syk on tyrosine. Notably, Syk promotes the clearance of SGs through autophagy, enhancing the ability of cells to survive the stress stimulus [98]. Besides, knockdown of Survivin, an anti-apoptotic molecule, is found to activate autophagy signal, along with the increased number of SGs [99]. It needs further study to reveal whether the activated autophagy signal associated the clearance of SGs and promote malignant cells survive.

Stress granules are the intersections of cell signaling pathways: mTOR signaling pathway as a paradigm

It's no exaggeration to say that SGs are the intersections of multiple molecules, while regulated signaling pathways are also potent to influence tumor initiation and progression, as well as chemotherapy drugs efficacy (**Figure 3**).

The activation of mTOR-S6 kinase pathway facilitates malignant progression of malignant tumor [100], and also promotes SGs assembly. S6K1 influence SGs number and size after mild arsenite treatment, while S6K2 may play a major role in the persistence of SGs, which is mTOR dependent and independent. In mechanism, the mTOR-S6 kinase pathway can promote SG assembly in response to mild oxidative stress by eIF2α phosphorylation [101]. Moreover, mTOR/4EBP1/eIF4E axis enhances the ability of SGs assembly [16]. Interestingly, lack of ataxin-2 (a component of SGs) increases phosphorylation of RPS6 and 4E-BP1 through the PI3K/mTOR pathway [102]. Given that malignant cancer cells require mTOR complex 1 (mTORC1) activity, hyperactivation of mTORC1 may lead to cells apoptosis, mTORC1 activity needs to be balanced in cancer cells [103]. Upon stress, the mTORC1 component raptor can be recruited to SGs, thereby preventing mTORC1-hyperactivation-induced apoptosis [104]. The findings hint that SGs are the intersections of mTOR signaling pathway, which can regulate SGs assembly; its component can be sequestered in SGs; in turn, other SGs component can influence the activation of mTOR signaling pathway. In fact, overexpression of the SG-neucleating protein (G3BP1), SG-formation-regulation protein (YB1) and mTOR signaling member can together predict poor clinical

prognosis of non-small cell lung cancer patients [105].

Reversely, another viewpoint suggest that mTORC1 is a main activator of translation, and thus translation arrest through mTORC1 inhibition via nutrient deprivation or small molecule compounds may has potential to induce SGs assembly [22, 106]. Controversially, in the model of chronic nutrient starvation, SGs assembly is not directly dependent on decreased mTORC1 activity, and is likely eIF2α phosphorylation dependent [107]. Remarkably, ethanol, inhibition of mTORC1 activity and complex formation, induces the formation of SGs; while INK128, complete inhibition of mTORC1 and mTORC2 activity, suppress the SGs formation in large B-cell lymphoma [108]. Although there is no consistent conclusion for the relationship between mTOR and SGs assembly, the initiation of malignant tumor apparently favor the first perspective. Given that the activation of oncogenic signaling to mTORC1 may facilitate cells grow, meanwhile, mTOR signaling pathway promotes SG assembly to resist adverse conditions and survive from chemotherapy.

In the process of SGs assembly, mTOR is regulated by traditional PI3K/AKT, but also by MAPK signaling pathway. It is reported that PI3K is the main driver of SGs when highly active, and the impact of MAPK/p38 becomes more apparent following PI3K activity declines [109]. Interesting, when SGs assemble, it negatively regulates apoptotic response by segregating RACK1, a scaffold for JNK/MAPK signaling, and thus suppress activation of the MTK1 (a MAPKKK)/JNK/MAPK pathway, which is a potential mechanism to cause chemotherapy [52].

Targeting stress granules assembly may influence the efficacy of chemotherapy drugs

Multiple chemotherapy drugs are potential to cause SGs assembly, and in turn, the formation of SGs may contribute to chemotherapy resistance by a series mechanism. It seems to be a promising target to reverse or avoid resistance of chemotherapy by inhibiting SGs assembly (**Figure 4**).

Targeting SG-nucleating proteins

SG-nucleating proteins, such as G3BP1 and CAPRIN1, are significant for the assembly of SGs and targeting their expression may be a potential strategy to partially reduce chemotherapy resistance caused by SG formation. When silencing G3BP1 mRNA and protein expression in U87 cells, the SG assembly is reduced and the bortezomib-treated cells have a significant increase in the apoptotic response with increased Caspase-3. Moreover, the conditioned culture medium of G3BP1-knocked-down bortezomib-treated cells inhibited angiogenesis compared to control group [78]. It is also reported that CAPRIN1 overexpression protects cancer cells from AS, or docetaxel-induced cell death, while CAPRIN1 knockout sensitizes malignant cells to stress-induced cell death. In the animal model, knockout of CAPRIN1 significantly reduced the growth of tumor xenografts [33].

Targeting eukaryotic translation initiation factors

In most cases, phosphorylation of eIF2α is the initial point of SGs assembly, and thus targeting its phosphorylation process seems to be an effective method to avoid SG-induced survival of malignant cells, enhancing the efficacy of chemotherapy drugs. Cancer cells are exposed to hypoxia in rapidly growing tumors, which increases production of ROS and induces SG formation. Hypoxia induces eIF2α phosphorylation and SG formation, resulting HeLa cells not sensible to cisplatin and paclitaxel. When partially reversing SG assembly by stanolone, HeLa cells are observed more sensible to cisplatin and paclitaxel under hypoxia [96]. Similar enhanced chemotherapeutically-induced cell death can be observed in glioma cells response to bortezomib, cisplatin, and etoposide [43]; MCF7 and HeLa cells to bortezomib [80]; U87 cells to ATO [66]. Silencing PERK, eIF2α kinase, also reverses resistance to ER stress and chemotherapy [110]. These results strongly indicate that Interfering eIF2α and its kinases may be a potential strategy for new co-adjuvant therapies to treat malignant tumors.

Apart canonical eIF2α phosphorylation, other eukaryotic translation initiation factors also facilitate SGs formation such as eIF4A in mutant KRAS cells following exposure to stress-inducing stimuli. It is observed that cell non-autonomous upregulation of SGs by mutant

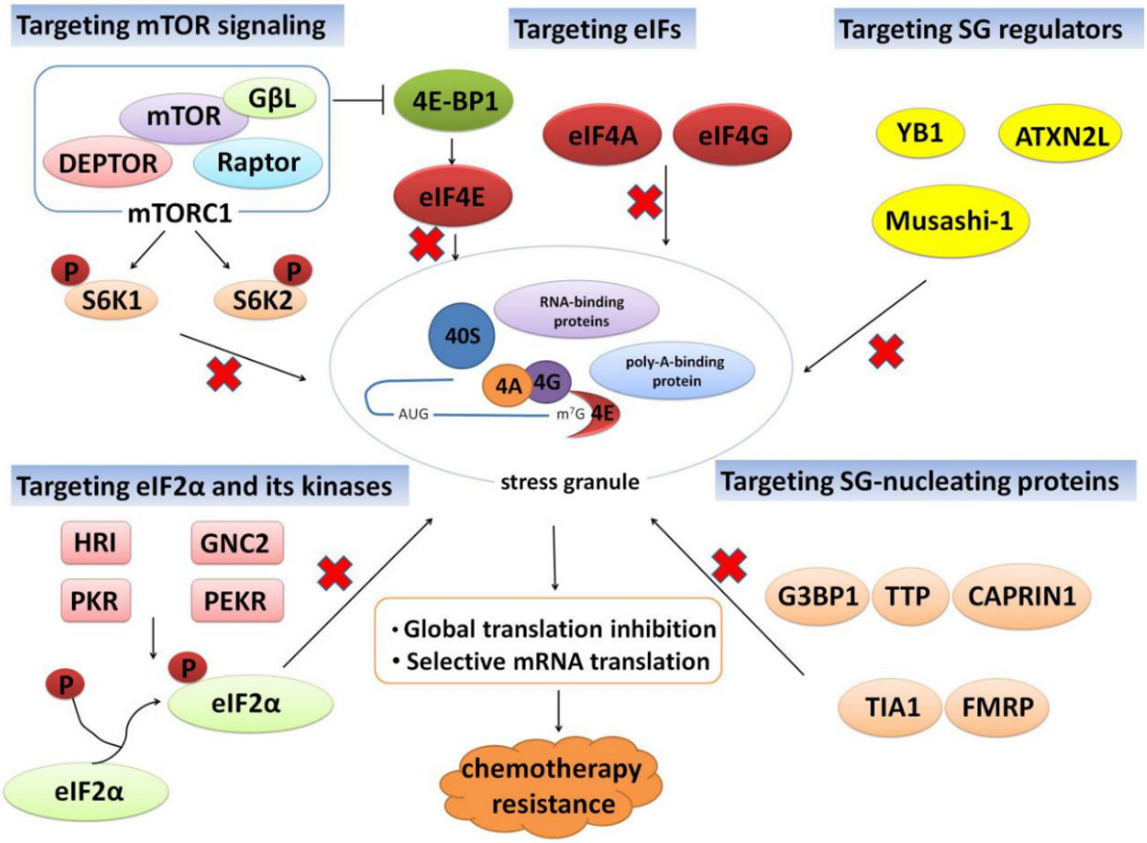

Figure 4. Targeting stress granules assembly may influence the efficacy of chemotherapy drugs. Targeting SG-nucleating proteins, eIF2α and its kinases, other eukaryotic translation initiation factors, and mTOR signaling may influence the SGs formation and the efficacy of chemotherapy drugs.

KRAS confers cells the resistance to oxaliplatin [111]. In fact, eIF4A is upregulated in colorectal cancer and predicts poor survival of patients, and knocking-down EIF4A2 sensitizes tumor cells to oxaliplatin treatment [112]. Besides, eIF4E is essential in the selenite-induced SGs assembly [31], and it may enhance efficacy or overcome drug resistance in combination with 5-FU, cisplatin and ATO [113-115]. These findings suggest targeting eIFs as a promising way for cancer treatment.

Targeting mTOR signaling

Although a small amount studies indicate that translation arrest through mTORC1 inhibition may has potential to induce SGs assembly (discussed before) [22, 106], more studies verify that mTOR signaling facilitates malignant progression of malignant tumor and also promotes SGs assembly. The later construct the basement of malignant phenotype and chemotherapy resistance of malignant tumors, and provide a feasible scheme for targeting mTOR signaling to enhance chemotherapeutic drug efficacy. It is proved to be influenced on gene translation by ethanol (inhibition of mTORC1 and induction of SGs) or INK128 (complete inhibition of mTORC1 and mTORC2 activity and suppression of SGs) in protein synthesis, cell cycle, proliferation and apoptosis [108]. It is well known that enhanced efficacy can be achieved by inhibition of mTOR, a primary resistance factor [116, 117], and whether the assembly or disassembly of SGs participate in this process needs to be further explored. Besides mTOR-S6 kinase pathway, mTOR/4EBP1/eIF4E also participate the assembly of SGs. It is reported that mTORC1-induced eIF4E-eIF4GI interactions facilitate SGs formation, while 4EBP1 inhibits mTORC1-dependent SGs formation by disrupting eIF4E-4GI association. Suppression of SG though depletion of eIF4E and eIF4GI sensitizes cancer cells to bortezomib-mediated apoptosis, involving p21 downregulation [16]. Therefore, there are still lots of work to be done

to verify how mTOR signaling influences the chemotherapy resistance in the future.

Conclusions and future perspectives

The assembly of SGs is a conservative strategy for cells to conserve energy and cope with adverse conditions. SGs formation may decrease global proteins synthesis, permitting specific pro-survival mRNA to translate to proteins, and thus ensure cells to survive in numerous stimuli. In fact, SGs widely participate in the physiological and pathological process of cells, playing oncogenic roles via influencing protein translation, proliferation, cell cycle, apoptosis, *et al*. In response to radiation [118] or chemotherapy drugs, SGs assembly may protect malignant cells to avoid lethal attacks and generate resistance to the treatment. SGs contribute to chemotherapy resistance by various mechanisms, such as facilitating ABC family expression, enhancing stemness of malignant cells and regulating cell apoptosis and autophage. In fact, YBX1 is regarded as the crossroad of P granules, SGs and exosomes, and seems to be a bridge of these non-membrane constructions [119]. Particularly, SGs form spontaneously in the cells with KRAS mutation, which may partially explain the primary drug resistance for some cancer patients. SGs can be induced by various kinds of chemotherapy drugs, in turn, the formation of SGs can decrease therapeutic effects and cause acquired chemoresistance.

The process of protein translation and SGs formation is complicated, and regulated by intrinsic and environmental factors. The activation of eIF2α kinases and phosphorylation of eIF2α is regarded as beginning points of SGs formation, also a few are eIF2α-independent, and other eukaryotic translation initiation factors or mTOR signaling involve. “Core first” model and “LLPS” model are constructed to explain why and how SGs assembly, and either one highlights the irreplaceability of nucleating proteins such as TIA-1 and G3BP1, which highly express in the malignant tissues than the adjacent and indicate the poor prognosis.

In the future, further researches have to be based on the omics analysis, studying the proteomics and metabonomics within and out of SGs. Moreover, SGs are a pool of mRNP, RNA binding proteins, eukaryotic translation initiation factors, poly-A-binding protein and ribosomal subunits, and are the intersections of cell signaling pathways. Therefore, the roles and functions of SGs are complicated and dynamic. More studies about SGs and chemotherapy resistance can be concentrated on the following aspects: (1) clearing the triggering mechanism of SGs coping with chemotherapy drugs, and developing the corresponding targets to avoid SG formation; (2) exploring the possibility of chemotherapy drugs and confirming the dose and time; (3) seeking the mutation of forming SGs spontaneously, and providing the evidence of primary resistance to chemotherapy; (4) studying how the formation of SGs influence the protein expression of proliferation, cell cycle and apoptosis, and partially explaining how acquired resistance to chemotherapy happens; (5) finding the relationship between SGs formation and drug resistance related proteins, such as P-glycoprotein, MRP, BCRP and LRP; (6) facilitating SGs formation in normal tissues to decrease the side effect of chemotherapy; (7) revealing the crosstalk between SGs and other membrane or non-membrane constructions.

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Disclosure of conflict of interest

None.

Abbreviations

SG, stress granule; ER, endoplasmic reticulum; mRNP, messenger ribonucleoprotein; HRI, heme-regulated inhibitor; PKR, protein kinase R; PERK, PKR-like endoplasmic reticulum kinase; GCN2, general control non-depressible 2; LLPS, liquid-liquid phase separation; IDR, intrinsically disordered protein region; ROS, reactive oxygen species; ATXN2L, Ataxin-2-like; 5-FU, 5-Fluorouracil; ISR, integrated stress response; ATO, arsenic trioxide; SA, sodium arsenite; ATRA, all-trans-retinoic acid; MTA, microtubule-targeting agent; MDR1, multidrug resistance 1; PKC, protein kinase C; CSC, Cancer stem cell; EMT, epithelial-to-mesenchymal transition.

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