iScience

CellPress
OPEN ACCESS

Review

Stress granules in cancer: Adaptive dynamics and therapeutic implications

Yunlu Jia,[1,5] Ruyin Jia,[2,5] Zhengfeng Dai,[3,5] Jianbiao Zhou,[4] Jian Ruan,[1] WeeJoo Chng,[4] Zhen Cai,[3,*] and Xiaochen Zhang[1,*]

SUMMARY

Stress granules (SGs), membrane-less cellular organelles formed via liquid-liquid phase separation, are central to how cells adapt to various stress conditions, including endoplasmic reticulum stress, nutrient scarcity, and hypoxia. Recent studies have underscored a significant link between SGs and the process of tumorigenesis, highlighting that proteins, associated components, and signaling pathways that facilitate SG formation are often upregulated in cancer. SGs play a key role in enhancing tumor cell proliferation, invasion, and migration, while also inhibiting apoptosis, facilitating immune evasion, and driving metabolic reprogramming through multiple mechanisms. Furthermore, SGs have been identified as crucial elements in the development of resistance against chemotherapy, immunotherapy, and radiotherapy across a variety of cancer types. This review delves into the complex role of SGs in cancer development and resistance, bringing together the latest progress in the field and exploring new avenues for therapeutic intervention.

INTRODUCTION

In the field of cell biology, understanding how cells respond to various stress conditions has been continuously deepening. In recent years, non-membranous cellular organelles—stress granules (SGs)—have become a hot topic of research. Indeed, SGs are formed through liquid-liquid phase separation (LLPS) and have the capability to assist cells in adapting to a variety of stress conditions, such as endoplasmic reticulum (ER) stress, nutrient deprivation, and hypoxia. SGs serve as sites for the temporary sequestration of messenger RNA (mRNA) and proteins.[1] Structurally, SGs consist of a dense core surrounded by a more dynamic shell, facilitating the selective recruitment and release of specific RNAs and proteins. Key components of SGs include various RNA-binding proteins (RBPs) like TIA-1, G3BP1, and eIF4G,[2,3] as well as stalled pre-initiation complexes and specific mRNAs. This intricate composition allows SGs to modulate translation, protect RNA integrity, and influence cell survival pathways during stress, marking them as pivotal regulators of cellular homeostasis. Additionally, SGs are dynamic structures, and the formation of SGs is reversible. When the stress stimuli are eliminated or the cell successfully adapts to the stress, the need for SGs diminishes. The components that had aggregated into granules, such as proteins and RNAs, are then released back into the cytoplasm. This rapid and efficient disassembly of SGs is crucial for the cell to recover its normal physiological state and maintain cellular homeostasis following stress resolution.

Tumor cells exist in a persistent state of stress due to their heightened metabolism, rapid growth, and altered microenvironment.[4] Notably, increasing evidence suggests that SGs support the development and spread of tumors by promoting cancer cell proliferation, invasion, and migration, while simultaneously hindering apoptosis. The content of SGs includes numerous molecules that are directly implicated in tumorigenesis.[5–7]Among these components, notable are oncogenes and tumor suppressor genes, as well as key regulatory proteins involved in cell growth and survival pathways, such as G3BP, components of the mTOR signaling complex, and HDAC6.[8–10] Meanwhile, the presence of SGs in tumor cells not only enhances the adaptability of tumor cells to harsh microenvironments but also provides them with a strategy to obtain cancer treatment resistance, particularly resistance to chemotherapy, immunotherapy, and radiotherapy.[11,12] This resistance partly arises from the protective role of SGs under drug exposure, allowing cancer cells to temporarily halt the synthesis of key proteins and thus survive under therapeutic pressure.

This review aims to delve into the multifaceted roles of SGs in tumor biology, particularly how they affect the survival mechanisms, invasive behaviors, and resistance to existing treatments of tumor cells. By integrating current research advancements, we aim to illuminate the prospects of targeting SGs as a strategy for cancer treatment, as well as their potential impact on future approaches to cancer therapy.

[1]Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[2]The Second School of Clinical Medicine of Zhejiang Chinese Medical University, Hangzhou 310053, China
[3]Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[4]Cancer Science Institute of Singapore, National University of Singapore, Singapore 117599, Republic of Singapore
[5]These authors contributed equally
*Correspondence: caiz@zju.edu.cn (Z.C.), zhangxiaochen@zju.edu.cn (X.Z.)
https://doi.org/10.1016/j.isci.2024.110359

THE STRUCTURE AND MAIN COMPONENTS OF STRESS GRANULES

SGs are dynamic structures composed of RNA and proteins, including RBPs and translation initiation factors. Normally, the assembly of SGs is facilitated by LLPS, a process driven by multivalent interactions among SG components.[5] The structure of SGs exhibits distinctive LLPS characteristics, comprising a stable core region and a dynamic shell region. Indeed, the core region of SGs is highly condensed, consisting of a large number of RBPs, translation initiation factors, ribosomal substrates, and translationally stalled mRNAs, forming an extensive network of mRNA-protein interactions. In addition, the shell region of SG is relatively sparse but remains in a liquid state with phase separation properties.[13] These two regions exhibit different kinetic properties in exchanging components with the cytoplasm and may have distinct compositions and functions. Recently, a study by Zhou et al. reports on a unique type of non-canonical SGs, called DHX9 SGs, that form in response to ultraviolet (UV)-induced RNA damage. Unlike typical SGs that accumulate mRNAs, these DHX9-containing granules are enriched with damaged intronic RNA. This highlights the presence of non-standard SGs that do not follow the conventional mRNA accumulation pattern and adds to our understanding of the complexity in stress response mechanisms.[14]

Key RBPs involved in SG formation include G3BP, TIA-1, TIAR, TDP-43, FUS, FMRP, and others, which harbor low-complexity domains and intrinsically disordered regions (IDRs), facilitating interactions with mRNAs and other SG components. Notably, RBPs act as nucleators, initiating the assembly of SGs by binding to specific RNA sequences or secondary structures.[15] Specifically, G3BP is a central component in the assembly and regulation of SGs. G3BP's interaction with partners like Caprin-1 and USP10 demonstrates the intricate balance in the formation and dissolution of SGs. While Caprin-1 facilitates SG assembly, USP10 suppresses it.[16] The latest research shows that the N-terminal and C-terminal domains of Caprin-1 can inhibit and promote SG assembly by affecting LLPS.[17] The activities of G3BP are fine-tuned by these interactions, as well as by its own post-translational modifications, which can modulate its ability to engage in phase separation and SG assembly under different stress conditions.[18]

Translationally stalled mRNAs represent a major constituent of SGs. These mRNAs typically possess stalled ribosomes due to stress-induced inhibition of translation initiation or elongation. While initially considered as a byproduct of global translation suppression, it is now evident that not all translationally repressed mRNAs are included in SGs. Instead, SGs selectively incorporate a specific subset of mRNAs, which tend to be longer and contain AU-rich elements within their sequences. These RNAs often encode for proto-oncogenes and are found to be consistently targeted to SGs across different types of cellular stress, suggesting a role beyond mere storage of untranslated mRNA.[19,20] In addition to stalled mRNAs and RBPs, SGs harbor a subset of translation initiation factors essential for protein synthesis initiation, including eIF2α, eIF3, eIF4A, eIF4B, eIF4E, and eIF4G. These initiation factors are typically involved in assembling the ribosomal preinitiation complex (PIC) under normal cellular conditions but become sequestered within SGs under stress conditions, which effectively stalls the translation initiation process and contributes to the global translational repression seen during cellular stress responses.[21] The phosphorylation status of eIF2α plays a pivotal role in SG assembly. Its phosphorylation by kinases such as HRI, PKR, PERK, and GCN2 is crucial for the formation of SGs. This modification is central to the mechanism that stalls translation initiation during stress.[22] Notably, eIF4G serves as a scaffold for assembling other initiation factors like eIF4E and eIF4A, along with other components of the translation initiation machinery on the mRNA. Its incorporation into SGs during stress interrupts cap-dependent translation initiation, highlighting its role in the selective sequestration process within SGs.[23–25] The presence of eIF4E in SGs, known for binding to the cap structure at the 5′ end of mRNAs, indicates that cap-bound mRNAs are also sequestered during stress. Thus, this suggests a mechanism by which cells prevent untimely translation of certain mRNAs under adverse conditions.[26] Beyond RNA and protein components, SGs may also contain aggregated proteins, particularly under prolonged or severe stress conditions.[27] These protein aggregates often consist of misfolded or damaged proteins targeted for degradation or sequestration, further highlighting the role of SGs in maintaining cellular proteostasis. Furthermore, both small (40S) and large (60S) ribosomal subunits are present in SGs, indicating their involvement in translational reinitiation once stress conditions subside.[28] Notably, while RBPs are pivotal in nucleating SG assembly by binding to specific mRNA targets, proteins lacking RNA-binding domains are also recruited through protein-protein interactions, further enriching the SG milieu. Consequently, the dynamic nature of SGs enables rapid assembly and disassembly in response to changing cellular conditions, allowing cells to swiftly adapt to environmental stresses.[29]

Furthermore, SGs also interact with lysosomes, ER stress responses, autophagy, and other intracellular homeostatic mechanisms, collectively maintaining the internal equilibrium of the cell.[30,31] Research has shown that SGs play a critical role in stabilizing damaged endolysosomal membranes. Specifically, they are implicated in endolysosomal membrane repair by plugging membrane breaches and promoting stability. Following lysosomal damage, components of SGs like G3BP1 and G3BP2 are quickly recruited to the site of injury, potentially facilitating membrane stabilization and aiding in the recruitment of repair machinery.[32] Additionally, SGs are connected to the ER stress response, another fundamental aspect of cellular homeostasis. SGs may influence ER homeostasis either directly or indirectly through their association with factors that regulate ER stress responses. SGs are also responsive to infection by pathogens like mycobacterium tuberculosis (Mtb), where they are formed in macrophages as a defense mechanism.[33] Infection-induced membrane damage triggers SG formation, potentially as a means to mitigate the spread of infection by interfering with pathogen survival and replication. Importantly, SGs can also interface with mTOR regulation, a central controller of autophagy and protein translation, via membrane atg8ylation during lysosomal stress.[34] Ultimately, this coupling of SG formation and mTOR inhibition ensures a coordinated response to maintain protein synthesis and overall cellular health.[30–34]

THE DYNAMIC ASSEMBLY AND DISASSEMBLY PROCESS OF STRESS GRANULES

SG assembly involves a tightly regulated process initiated by cellular stress, leading to the formation of dynamic structures that play a crucial role in cellular responses to environmental challenges.[35] Actually, the assembly of SGs can be divided into two categories according to

whether it is eIF2α-dependent phosphorylation, namely canonical assembly and canonical assembly.[36,37] Classical phosphorylation of assembled eIF2α is usually induced by oxidative stress, heat shock, etc.[38] eIF2α forms a ternary complex with guanosine triphosphate (GTP) and Met-tRNAmiet6 upon translation initiation. With the formation of the ternary complex, the part of the 40S ribosomal subunits eIF1, eIF1A, eIF3, and eIF5 will combine with the eIF2-GTP-Met-tRNAmietarycom-complex to form the PIC, the 43S pre-initiation complex. The 5′-proximal region of the mRNA is then uncapped by the eIF4F complex and eIF4B, a process that relies on the involvement of ATP. Next, the 43S PIC binds to the mRNA and recognizes it in the 5′-3′ direction following the start codon. After the recognition is completed, 43S PIC will change its conformation to form 48S PIC. If the cell is under stress, translation will be inhibited, which is related to key molecules in the initiation process. Once translation is inhibited, the core structure of the SG is formed by protein-protein interactions and IDR potential fibrils promoted by higher concentrations of messenger ribonucleoprotein (mRNP) within the shell. In addition, some studies have also observed that when entering SG, translationally inactive mRNA becomes tightly compressed and its movement is restricted.[39,40] Atypical SG assembly represents a pathway that forms SGs independent of eIF2α phosphorylation. This alternative pathway can be triggered by various cellular stresses that do not necessarily lead to eIF2α phosphorylation but still require the cell to modulate translation and protect mRNA molecules. Certain stressors or compounds can lead to SG formation by disrupting the eIF4F complex, consisting of eIF4A, eIF4E, and eIF4G, which is essential for cap-dependent translation initiation.[41] Disruption of eIF4A activity, for example, through the action of small molecules or RNA helicase inhibitors, can dissociate the complex and promote SG assembly without affecting eIF2α phosphorylation. Additionally, studies have shown that SG assembly can be triggered by alterations in other components of the translation machinery, such as the eIF4E-binding proteins (4E-BPs) or through the direct modulation of mTORC1 signaling, which can influence eIF4F complex activity.[41] In certain instances, stressors like selenite and certain chemotherapy drugs can induce SGs through mechanisms that bypass eIF2α phosphorylation. For instance, selenite has been shown to interfere with the eIF4E pathway by modulating eIF4E-binding protein 1.[42,43]

More recently, SGs have been conceptualized through the lens of liquid-liquid phase separation (LLPS). This model suggests that SGs form via a process akin to how oil separates from water. Certain RBPs, when exposed to stress conditions, undergo conformational changes or multimerization that increases their hydrophobicity and drives them to phase separate from the surrounding cytoplasm, forming droplets. These droplets attract and concentrate specific mRNAs containing SG-localizing sequences, leading to SG formation.[44] IDRs within proteins resident play a crucial role in the aggregation and formation of SGs.[5] IDRs are segments of proteins that lack a fixed or ordered three-dimensional structure under physiological conditions. These regions are highly flexible and can adopt multiple conformations, allowing them to participate in a wide range of protein-protein and protein-RNA interactions. IDRs can drive the process of LLPS, which is fundamental to the formation of SGs. LLPS allows for the demixing of cellular components into two phases, leading to the concentration of SG proteins and RNA into dense assemblies. The flexibility and dynamic nature of IDRs allow them to mediate interactions with multiple partners, including other SG proteins and RNA molecules, as well as for the structural organization of SGs. Additionally, post-translational modifications (PTMs) on the IDRs, such as phosphorylation, acetylation, SUMOylation, etc., can alter the charge, hydrophobicity, or create additional interaction interfaces of IDRs.[44–46] This further influences the strength and selectivity of interactions between proteins, thereby regulating the assembly, maturation, disassembly, and response to external stimuli of SGs.

The breakdown of SGs after the dissipation of stress is indeed a step-by-step process, reflecting the highly regulated nature of SG dynamics. This disassembly is crucial for restoring normal cellular function by releasing mRNAs and proteins sequestered within SGs for translation or other cellular processes. The initial trigger of SGs dissociation is the alleviation of the stress condition. Research indicated that the dephosphorylation of eIF2α, a critical regulator of SG formation under stress, is one of the primary signals for SG disassembly.[47]During the dissociation process, kinases such as DYRK3, through their dual-specificity kinase activity, are linked to the mTORC1 signaling pathway, regulating the condensation and dissolution of SGs.[48,49] ULK1 and ULK2 promote the disassembly of SGs by phosphorylating and activating the VCP/p97 protein.[50] Additionally, the deubiquitinating enzymes OTUD4 and ZFAND1 of the ULP1 family are involved in the clearance of stress-induced SGs by recruiting p97/VCP and 26S proteasomes, highlighting the importance of SG degradation and disassembly.[51] Meanwhile, protein modifications such as arginine methylation, ubiquitylating, and methylation profoundly influence the fate of SGs.[52–56] For example, arginine methylation of the G3BP1 protein facilitates its release from SGs, thereby promoting SG resolution. Conversely, the demethylase JMJD6 indirectly facilitates SG assembly and maintenance through its demethylation activity on G3BP1.[8] Additionally, the methylation status of the arginine-glycine-glycine-rich repeat (RGG motif) region of AGO1, a member of the ARGONAUTE family, similarly affects the localization and formation of SGs. The monitoring role of the heat shock protein chaperone system, such as the HSPB8-BAG3-HSP70 complex, is crucial for maintaining the integrity and dynamics of SGs.[57] This complex helps SGs return to their normal state after stress or facilitates the orderly dissolution of SGs at the appropriate time. IDRs within SG proteins undergo changes in interactions that lead to the disaggregation of SGs. Molecular chaperones and disaggregases may assist in this process by altering the interactions between IDR-containing proteins and RNA molecules, facilitating the breakdown of the dense phase. As the interactions within SGs are reversed, RNA molecules, including mRNAs, and proteins start to be released from the granules.[58]

Disassembly of SGs is governed by context-specific mechanisms, which can involve either autophagy-dependent or autophagy-independent pathways depending on the type and duration of the stress stimulus. This final cleanup ensures that all traces of SGs are removed, allowing the cell to fully recover from the stress condition. Studies systematically investigated well-defined autophagy receptors and identified important roles for endogenous SQSTM1/p62 and CALCOCO2/NDP52 in SG elimination.[32] In some cases, SG disassembly is triggered by ubiquitination events, particularly in the context of heat shock, where the RBP G3BP1 becomes polyubiquitinated, allowing for its extraction from the SG network by the ER-associated protein FAF2 and subsequent engagement of the ubiquitin-dependent segregase VCP/p97.[9] This extraction weakens the interaction network holding the SG together, causing it to fall below the percolation threshold necessary for phase

separation and leading to granule disassembly. Additionally, overexpression of TRIM21, a central regulator of SG homeostasis, inhibits SG formation. The mechanism is related to the K63-linked ubiquitination of the SG core protein G3BP1.[32] Other factors such as pH changes, proteasomal degradation machinery, and modulation of specific PTM (like phosphorylation, ubiquitination, and SUMOylation) also influence SG dynamics and turnover.[59–61] SGs can act as buffers for the ubiquitin-proteasome system, potentially preventing proteotoxic stress in the nucleus by sequestering damaged proteins and facilitating their eventual disposal. SG disassembly can be regulated by the involvement of specific adaptor proteins like ZFAND1, ATPases like VCP/p97, and enzymes like deubiquitinating enzymes (DUBs) that remove ubiquitin moieties from granule components.[62] As shown in Figure 1, the assembly and disassembly of SGs are vital components of the cellular stress response mechanisms.

MOLECULAR FUNCTIONS OF STRESS GRANULES IN CANCER BIOLOGY

The formation of SGs is anticipated to influence tumor biological responses in several significant ways, fundamentally reshaping how cancer cells react to diverse stress conditions and therapeutic interventions. Firstly, RBPs such as G3BP1/2,[63,64] TIA-1,[65] and FMRP[66] within SGs recognize specific RNA motifs and can alter the stability, localization, and translation of these mRNAs, which provides a new gene regulation perspective for cancer survival and proliferation. The second way is to limit the interaction of the separated components with the bulk cytosol. SGs form in response to cellular stress, including oxidative stress, hypoxia, and chemotherapeutic agents, common in the tumor microenvironment. This mechanism allows cancer cells to survive under adverse conditions by conserving resources and selectively translating stress-response proteins. Various roles of main components of SGs in various cancer types were summarized in Table 1.

Biology of cancer affected by stress granules' interaction with RNA-binding proteins

Ras GTPase-activating protein-binding protein 1 (G3BP1), alongside its paralog G3BP2, is a critical nucleator of SGs due to its ability to initiate and maintain SG formation through its interaction with the 5′ untranslated region (UTR) of mRNAs and other SG components.[67] Upon stress induction, G3BP1 undergoes a conformational switch that exposes its arginine-rich (RG) and glycine-rich regions, enabling it to interact with RNA molecules and other SG-nucleating proteins, such as Caprin-1 and TIA-1/TIAR.[16] Additionally, G3BP1 is subject to post-translational modifications, such as K63-linked ubiquitination, which contributes to the modulation of SG assembly and disassembly.[67] TRIM21 and USP10 mediate the ubiquitination and deubiquitination of G3BP1, respectively, to influence SG dynamics and stability.[68]Phosphorylation events, such as serine 149 phosphorylation of G3BP1, can also modulate SG assembly and disassembly.[69] Moreover, direct association of G3BP1 with 40S ribosomal subunits, particularly under stress conditions, points to a functional role in orchestrating the transition from active translation to SG assembly.[70]

In the context of tumor biology, G3BP1 is a multifunctional protein that plays a significant dual role in tumor biology, acting both as a tumor promoter and an essential regulator of SG assembly. G3BP1's involvement in numerous oncogenic signaling pathways, like Wnt, TGF-β/Smad, PI3K/AKT/mTOR, and IL-6/STAT3, contributes to aggressive tumor behavior, poor patient prognosis, and increased resistance to treatment across several cancer types.[71,72] Both G3BP1 and G3BP2 have been shown to interact with p53, influencing its localization and function. Fast tag

During lung cancer progression, G3BP1 interacted with lncRNA P53RRA to influence the p53 pathway and affect cellular apoptosis and metastasis.[73] G3BP1 has been shown to be a direct target gene of the androgen receptor (AR), a critical driver of prostate cancer growth and progression. Upon androgen stimulation, G3BP1 is induced, which contributes to the androgen-dependent translocation of p53 from the nucleus to the cytoplasm. This nuclear export of p53 is facilitated by G3BP1 interacting with the SUMO E3 ligase RanBP2, promoting p53 sumoylation.[74] G3BP2 has been implicated in the androgen-mediated nuclear export and sumoylation of p53 in prostate cancer, impacting the balance between cell proliferation and apoptosis.[75] G3BP1 has been found to regulate the senescence-associated secretory phenotype (SASP) in prostate cancer cells, which is a set of secreted factors that can influence the tumor microenvironment and contribute to cancer progression. It can also activate the androgen (AR) signaling axis through the stabilization of AR and its co-activators like TRIM24, promoting tumor growth.[76]

Targeting G3BP1 could sensitize cancer cells to chemotherapy. G3BP1 influences apoptosis by regulating the stability of programmed death ligand 1 (PD-L1) in gastric cancer, affecting patients' response to chemotherapy.[77] Depletion of G3BP1 sensitizes cancer cells to chemotherapy by enhancing apoptosis, and its interaction with YWHAZ has been found to play a critical role.[78]G3BP1 also regulates the redox balance within cancer cells by modulating the translation of NRF2, thus affecting the cells' ability to withstand oxidative stress.[79] In esophageal cancer, G3BP1 appears to be involved in SG formation during lysosomal damage and may contribute to stress responses and cell-cycle regulation.[80] In melanoma, G3BP1 was found to interact with LIM domain kinase 2 (LIMK2), a serine/threonine kinase overexpressed in melanoma. Through this interaction, G3BP1 helps stabilize and increase the expression of ESM1, which promotes tumor growth and metastasis.[81] Besides, G3BP2 has been linked to tumor initiation in breast cancer, where it regulates the expression of stem-cell-associated genes like Oct-4 and Nanog through its interaction with SART3, supporting tumor growth and proliferation.[82]

Heterogeneous nuclear ribonucleoproteins (hnRNPs) such as hnRNPA1, hnRNPA2B1, TIA-1, TIAR, and others are integral components of SGs, helping to regulate their assembly, stability, and disassembly.[83] These hnRNPs have been implicated in the regulation of mRNAs involved in stress responses and cancer progression. TIA-1 and TIAR, which contain RNA recognition motifs (RRMs) and a glutamine-rich prion-related domain (PRD), contribute to SG formation by recruiting untranslated mRNAs and promoting their aggregation. Specifically, the PRD of TIA-1 undergoes self-aggregation, a characteristic shared with prion proteins, and drives the condensation of SGs. TIA-1 and TIAR are involved in mRNA stability and translational control, linking eIF2α phosphorylation to SG assembly and mRNA sequestration.[83]

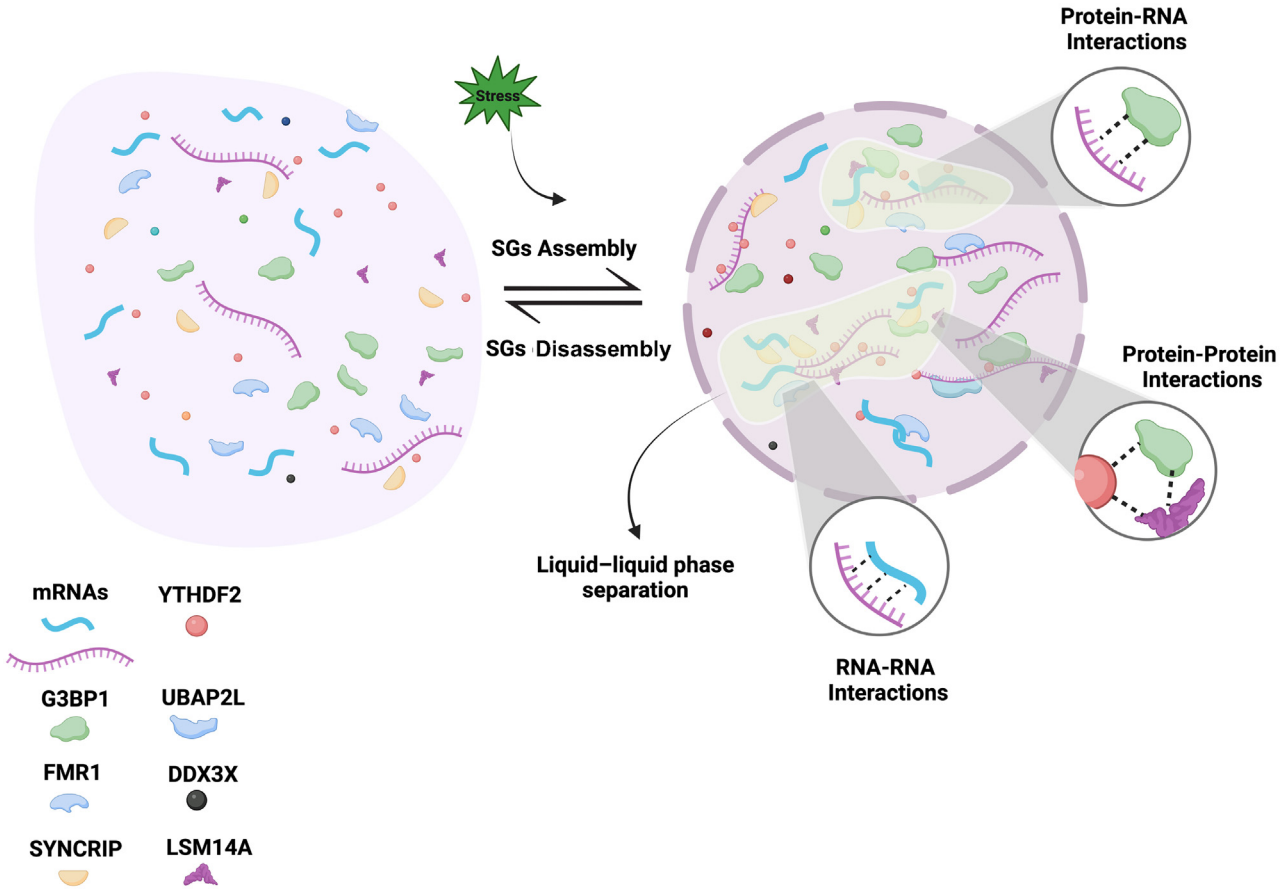

Figure 1. Model of SG assembly and disassembly

Upon cellular stress, RNA influx and key SG proteins (such as G3BP1, FMR1, SYNCRIP, YTHDF2, UBAP2L, DDX3X, and LSM14A) form a multi-interaction network, which facilitates liquid-liquid phase separation (LLPS), subsequently triggering the assembly of SGs. Following the alleviation of stress, the dissociation of protein-protein, protein-RNA, and RNA-RNA interactions within SGs leads to a reduction in the effective valency or binding capacity, thereby enabling the disassembly of SGs and the restoration of normal cellular function.

Additionally, studies have shown that perturbations in the regulatory mechanisms controlling SG assembly, such as mutations in TIA-1/TIAR or manipulation of their interactions with other proteins like G3BP1 and Caprin-1, can affect SG dynamics and impact cellular responses to stress.[84] The mechanism by which TIA1 inhibits cancer proliferation is related to the regulation of cell cycle by p53. Under stress conditions, RSK2 is recruited to SGs by TIA1. After RSK2 is broken down by SG, it reaches the nucleus where it interacts with cyclin D1 and becomes a catalyst for the relentless proliferation characteristic of cancer cells. During modest stress conditions,[85] TIA-1 and TIAR can suppress stress-induced apoptosis by recruiting and sequestering pro-apoptotic factors away from their targets, effectively buffering the cell against immediate death. For instance, they can limit the activation of stress-responsive MAPK pathways that initiate programmed cell death.[86]

The SG-associated proteins Caprin-1and USP10 bind mutually exclusively to the NTF2 domain of G3BP1, promoting and inhibiting SG formation, respectively.[60] Caprin-1itself can modulate SG formation and disassembly by interacting with G3BP1, and its specific domains seem to influence these processes differently. The C-terminal domain of Caprin-1 undergoes phase separation, which can lead to spontaneous SG formation, whereas its N-terminal domain and G3BP1-interacting motif can suppress SG disassembly. The complex formation is influenced by pH, with lower pH values destabilizing the Caprin-1/G3BP1 interaction, suggesting that the acidic environment within SGs could modulate SG dynamics.[60] Caprin-1 has been implicated in several aspects related to cancer cell proliferation, survival, and metastasis.[87,88] Specifically, CAPRIN-1 plays a crucial role in promoting the proliferation of hepatocellular carcinoma and breast cancer cells by increasing the expression levels of c-Myc and cyclinD1 mRNA.[65] In osteosarcoma, CAPRIN-1 can activate the Akt and ERK1/2 signaling pathways.[89] CAPRIN-1 overexpression of osteosarcoma has also been found to accelerate the transition from the G1 to S phase of the cell cycle, which is essential for tumor growth, and to enhance the expression of immune checkpoint proteins like CD47 and PD-L1. In relation to the immune response, Caprin-1 was associated with increased infiltration of $CD4^+$ T cells and tumor-associated macrophages (TAMs) in PDAC tissues, emerging as a critical regulator of disease's aggressive nature and poor prognosis.[87]

Tristetraprolin (TTP), also known as ZFP36, is an RBP involved in the regulation of mRNA stability and translation.[90] TTP has been found to localize to SGs under certain stress conditions, and its function is tightly intertwined with cellular stress responses and cancer biology. TTP has

Table 1. Various roles of stress granules-related factors in different cancer types

Cancer type	Downstream targets	Expression	Functions	Cell lines/Patient tissue/Murine mode
Non-small cell lung cancer	G3BP2	Up	Predicts drug response, immune response, and patients' prognosis	Bioinformatics approaches, human cell lines, mouse model, and human tissues
Non-small cell lung cancer	mTORC1	Up	Survives under low-lactate stress	Human cell lines
Breast cancer	SART3	Up	Breast cancer initiation	Mouse model and human tissue
Breast cancer	PI3K/PKCα/CK2α	Down	Cell proliferation inhibition	Human cell lines
Breast cancer	PI3K/p38	Up	Promotes cell survival	Human cell lines
Breast cancer with brain metastases	HSPs	Up	Reprograms tumor-associated macrophages and sensitizes photothermal therapy	Human cell lines and mouse model
Triple-negative breast cancer	PKR/eIF2α RACK1/MTK1	Up	Chemoresistance	Human cell lines, mouse model, and human tissues
Pancreatic ductal adenocarcinoma	IGF1/PI3K/mTOR/S6K1	Up	Promotes obesity-associated PDAC development	Human cell lines, mouse model, and human tissues
Pancreatic ductal adenocarcinoma	KRAS/P53	Up	Promotes resistance to gemcitabine and cancer progression	Human cell lines
Pancreatic ductal adenocarcinoma	KIF20A	Up	Promotes the motility and invasiveness of cancer cells	Human cell lines
Osteosarcoma	YB-1	Up	Enhanced oxidative stress and hypoxia-induced cell apoptosis	Human cell lines and mouse model
Sarcoma	NFE2L2/NRF2	Down	Suppresses sarcoma metastasis	Human cell lines and mouse model
Hepatocellular carcinoma	circVAMP3/Myc	Up	Chemoresistance and poor prognosis	Human cell lines, mouse model, and human tissue
intrahepatic cholangiocarcinoma	NF-κB	Up	Promotes progression	Human cell lines, mouse model, and human tissue
Head and neck squamous carcinoma	/	Up	Radiosensitive	Human cell lines
Head and neck squamous carcinoma	PRMT5-USP7-G3BP2	Up	Poor prognosis	Human cell lines, mouse model, and human tissue
Nasopharyngeal carcinoma	CCND2	Down	Inhibits proliferation and migration; increases sensitivity to cisplatin and X-rays	Human cell lines, mouse model, and human tissue
Renal angiomyolipoma	TSC2	Down	Suppresses cell growth	Human cell lines and mouse model
Subependymal giant cell astrocytoma	TSC2	Down	Suppresses cell growth	Human cell lines and mouse model
Colorectal cancer	ONC/TS	Up	5-FU chemoresistance and tumorigenesis	Human cell lines and human tissue
Colorectal cancer	MYC/AMPK/mTORC1	Up	Tumorigenesis and chemoresistance	—
Colorectal cancer	microRNAs/G3BP1/PD-L1	Up	Facilitates progression and immune escape	Human cell lines, mouse model, and human tissue
Gastric cancer	PI3K/Akt	Up	Oxaliplatin resistance and cell migration	Human cell lines and human tissue

(*Continued on next page*)

Table 1. *Continued*

Cancer type	Downstream targets	Expression	Functions	Cell lines/Patient tissue/Murine mode
Gastric cancer	G3BP1	Up	Regulates chemoresistance and predicts adjuvant chemotherapy benefit	Human cell lines and mouse model
Osteosarcoma	miR-124-3p/G3BP2	Up	Promotes cell survival	Human cell lines
Glioblastoma	PKR/eIF2α	Up	Grants cancer stem cell properties and chemoresistance	Human cell lines
Chondrosarcoma	IL-12	Up	Bystander effect	Human cell lines
Glioma	/	Down	Increases response to chemotherapeutic agents	Human cell lines
Oral squamous cell carcinoma	CCL13	Up	Tumorigenesis	Human cell lines and mouse model
Renal cell carcinoma	IL-6/G3BP1/STAT3	Down	Promotes cell proliferation, migration, and invasion; Sorafenib resistance	Human cell lines, mouse model, and human tissue
Head and neck squamous cell carcinoma cells	/	Up	Radiosensitive and radioresistant	Human cell lines
Kaposi's sarcoma	/	Up	Evades host antiviral immunity	Human cell lines
Astrocytoma	AurkB	Down	Enhances susceptibility to radiation and chemotherapy	Human cell lines
Prostate cancer	Caprin1	Up	Docetaxel resistance	Human cell lines, mouse model, and human tissue
Prostate cancer	p53/AR	Up	Cancer cell survival	Human cell lines
Prostate cancer	G3BP1	Down	Reduces PCA cell survival rate	Human cell lines
Laryngeal papilloma	miR-1224-5p/OGFOD1	Up	Tumorigenesis	Human cell lines
Melanoma	MDA5	Up	Reduces autophagy	Human cell lines
Melanoma	G3BP1-ESM1		Promotes tumor growth and metastasis	Human cell lines and mouse model
Uterine corpus endometrial carcinoma	IGF2BP1	Up	Cancer pathogenesis and progression	Bioinformatics approaches
Cervical cancer	galectin-7/RACK1/G3BP1	Down	Promotes cisplatin sensitivity	Human cell lines and human tissue
Esophageal squamous cell carcinoma	PURα	Up	Tumorigenesis	Human cell lines
Esophageal squamous cell carcinoma	Wnt/β-catenin/PI3K/AKT	Down	Suppresses proliferation, migration, and invasion capabilities	Human cell lines
T cell leukemia	ROS	Up	Reduces ROS production and inhibits ROS-dependent apoptosis	Human cell lines
Chronic myelogenous leukemia	BCR-ABL	Up	Contributes to BCR-ABL-dependent leukemogenesis	Human cell lines
BCR-ABL1 leukemia cells	BRCA1	Up	Genomic instability	Human cell lines

(*Continued on next page*)

Table 1. *Continued*

Cancer type	Downstream targets	Expression	Functions	Cell lines/Patient tissue/Murine mode
Chronic lymphocytic leukemia	mTORC1/MYC	Up	Decreases anti-IgM-induced translation and induces cell death	Human cell lines
Acute myeloid leukemia	CNST	Up	Diagnostic- and prognostic-related biomarker	Human cell lines
Myeloid malignancies	U2AF1/U2AF2	Up	Drivers of myeloid malignancies	Human cell lines
Medulloblastoma	DDX3X/DED1	Up	Tumorigenesis and cell translation	Human cell lines

been shown to play a role in the stress response by recognizing and binding to AU-rich elements (AREs) within the 3′-untranslated regions (3′UTRs) of labile mRNAs, marking them for degradation or translational repression.[91] In cancer, TTP demonstrates tumor-suppressive properties, as it negatively regulates the expression of several oncogenic and pro-inflammatory mRNAs, including those coding for cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2).[92] Research has shown that TTP is excluded from SGs in response to oxidative stress when it is phosphorylated by the MAPKAP kinase-2 (MK2), which promotes the assembly of TTP:14-3-3 complexes.[93] This exclusion is associated with a block in TTP-mediated mRNA decay, potentially contributing to the maintenance of pro-survival mRNAs in cancer cells and influencing their response to therapeutic agents. TTP has been shown to regulate the mRNA stability of c-Myc, a potent oncogene, and its downregulation can lead to the stabilization and increased expression of c-Myc in cancer cells.[94]

Fragile X mental retardation protein (FMRP) is a multifunctional RBP that is centrally involved in mRNA metabolism. Indeed, FMRP has been shown to regulate the phosphorylation state of eIF2α, a key player in the stress response that determines the extent of SG formation and global protein synthesis inhibition.[95] FMRP's interaction with the RISC complex and its effect on RISC efficiency are not direct, but rather FMRP associates with a specific pool of mRNAs that would otherwise be incorporated into SGs. Additionally, FMRP has been reported to be involved in the demarcation of mRNAs for stress-induced decay or storage by regulating the balance between translation repression and mRNA stability.[96,97] Additionally, FMRP plays a role in mediating tumor progression, immune evasion, and resistance to therapy. Studies have found that the absence of FMRP leads to a decrease in immunosuppressive factors and an increase in $CD8^+$ T cell infiltration, suggesting a role in suppressing immune responses against tumors.[66] FMRP is involved in the production of immunosuppressive factors like IL-33 and tumor-secreted protein S (PROS1) that can induce regulatory T cells and M2-like macrophages, creating an immunosuppressive microenvironment in tumors. Additionally, FMRP upregulation has also been associated with cancer stem cell properties and poor prognosis in glioblastoma and other cancers.[98]

YTHDF proteins, namely YTHDF1, YTHDF2, and YTHDF3, are a class of RBPs that specifically recognize and bind to N6-methyladenosine (m6A) modifications on mRNAs.[99] Recent research highlights that O-GlcNAcylation of YTHDF1 and YTHDF3 modifies their behavior in SGs, affecting granule assembly, stability, and dynamics. O-GlcNAcylation can inhibit the translation-promoting function of YTHDF1/3 by preventing their interaction with ribosomal components, which is crucial for mRNA translation initiation.[100] While YTHDF1 and YTHDF3 are mainly involved in translation promotion, YTHDF2 is known to promote mRNA decay by recruiting m6A-marked mRNAs to degradation machinery.[101] In cancer cells, the balance of YTHDF protein functions can be disrupted, contributing to altered mRNA metabolism that supports tumor growth and survival. High O-GlcNAcylation levels in certain cancer cells can dampen the translation-promoting effect of YTHDF1/3, which could affect how cancer cells respond to stress and translate specific mRNAs that promote survival or metastasis. YTHDF proteins have been linked to chemotherapy resistance, as they can mediate the translation or decay of mRNAs that regulate the DNA damage response or the Wnt/β-catenin pathway. In colorectal cancer, YTHDF1 enhances the metabolism of glutamine, which helps cancer cells resist cisplatin, and YTHDF3 can promote resistance to drugs by influencing mRNA translation in resistant cells. In liver cancer, YTHDF2 promotes the decay of SOCS2 mRNA, which when stabilized, restrains the Wnt/β-catenin pathway and tumor growth.[102]

Y-box binding protein 1 (YB-1) localizes to SGs, where it influences SG assembly by binding to and activating the translation of G3BP1 mRNA via its interaction with the 5′-UTR.[103] The cold shock domain of YB-1 allows it to destabilize RNA structures, enhance mRNA availability, and thus contribute to SG formation under stress conditions. Moreover, YB-1 binds to tRNA-derived small RNAs (tiRNAs) using the same cold shock domain, facilitating mRNA packaging into SGs without affecting tiRNA-mediated translation inhibition.[104] Research has also demonstrated that specific 5′-tiRNAs collaborate with YB-1 to displace the cap-binding complex eIF4F, consequently inhibiting translation initiation and promoting SG assembly. During arsenite stress recovery, YB-1 participates in SG disassembly, potentially linked to its role in the translational activation of HSP70 mRNA.[105] YB-1's activities significantly influence the malignancy and drug resistance of cancer. In gastric cancer, YB-1 interacts with Pur-α to mediate the oncogenic effects of the lncRNA gene TM4SF1-AS1 when marked by H3K4me3.[106] In breast cancer, reducing YB-1 expression can suppress cancer cell malignancy, and silencing CORO1C, a downstream target of YB-1, impairs cell migration and invasion.[107] Furthermore, YB-1 promotes the invasiveness of triple-negative breast cancer (TNBC) cells by binding to the MMP1 promoter and modulating β-catenin activity.[108] Beyond these direct roles in SG dynamics and cancer cell behavior, YB-1 also regulates malignancy and therapy resistance through various signaling pathways, including ERK/AKT/mTOR, PI3K/Akt, Snail, and MDM2/p53.[109–111]

Ubiquitin-specific protease 10 (USP10) contributes to the cellular antioxidant defense mechanism by inhibiting reactive oxygen species (ROS) production.[112] When cells experience arsenic-induced oxidative stress, USP10 is mobilized to SGs to mitigate ROS-dependent apoptosis. Its presence is essential for the formation of Tau/TIA1/USP10-positive SGs, as evidenced by the decreased induction of TIA1/Tau-positive SGs upon USP10 depletion in HT22 neuronal cells.[113] The dynamic interplay between Caprin1/USP10 and G3BP proteins is mutually exclusive and crucial in orchestrating the assembly and disassembly processes of SGs. Clinically, USP10 exhibits high cytoplasmic expression in prostate cancer cells, which is associated with a poor prognosis. This is partly due to USP10's regulatory influence on the p53-G3BP2 complex and AR signaling pathways.[114] Moreover, USP10 mediates the function of GF2BP1 to promote metastasis via m6A-dependent regulation of CPT1A in breast cancer. Additionally, USP10 interacts with circWSB1 in breast cancer, impacting the stability of p53 to foster cancer progression.[115] In pancreatic cancer, USP10 acts to protect cancer cells from apoptosis induced by ER stress.[116]

The AMP-activated protein kinase (AMPK) is a key energy sensor that exerts a significant influence on SG biology. Activation of AMPK leads to alterations in SG composition and size, which in turn can affect cell survival and various cellular processes like signaling pathways, cytoskeletal organization, and the levels of translation initiation factors.[117] Specifically, AMPK activation results in increased phosphorylation of eIF2α, concurrent with reductions in eIF4G and eIF4E.[118] The role of AMPK in cancer treatment resistance is multifaceted, encompassing actions such as the regulation of ABCG2 expression, autophagy induction, and the modulation of cancer stem cell populations.[119–121]

Metformin-activated AMPK was shown to alleviate H3K9me2-mediated repression of epithelial genes (like CDH1) during epithelial-mesenchymal transition, thereby inhibiting lung cancer metastasis.[122] Moreover, activated AMPK inhibits aromatase activity, thereby decreasing estrogen synthesis and limiting breast cancer growth.[123]

Histone deacetylase 6 (HDAC6) is a unique cytoplasmic deacetylase that has emerged as a vital constituent of SGs, interacting with the SG-nucleating protein G3BP and localizing to SGs.[124] HDAC6 appears to orchestrate SG formation by possibly facilitating the movement of SG components along microtubules through motor protein engagement. Using specific inhibitors, researchers have observed that approximately 35% inhibition of SG formation occurs with tubastatin A, a selective HDAC6 inhibitor.[125] HDAC6 has been implicated in the malignant proliferation and metastasis of several cancer types, such as colon, ovarian, liver, gastric, cervical, and breast cancers.[126] In bladder cancer, selective HDAC6 inhibition improves the effectiveness of radiotherapy and mitigates the CXCL1-Snail signaling cascade triggered by radiation.[127] Additionally, HDAC6 inhibitors can sensitize ovarian cancer to paclitaxel, triple-negative breast cancer to cysteine deprivation, and breast cancer to epirubicin treatment.[128]

Knockdown of KIF20A, a motor kinesin, inhibited the accumulation of IGF2BP3-containing SGs in cell protrusions and inhibited local protein expression of specific IGF2BP3-binding transcripts ARF6 and ARHGEF4. KIF20A promotes pancreatic cancer cell motility and invasiveness by transporting the RBP IGF2BP3 and IGF2BP3-binding transcripts.[129] IGF2BP3 and its target transcripts assemble into cytoplasmic SGs in pancreatic cancer cells, and IGF2BP3 promotes cell motility and invasiveness by regulating the local translation of IGF2BP3-bound transcripts in cell protrusions. SUCLA2, the succinyl-CoA ligase ADP-forming subunit β, is a constituent of SGs and participates in their assembly.[130] Research has revealed that SUCLA2 is a crucial mediator of anoikis resistance, the programmed cell death triggered by cell detachment from the extracellular matrix, and drives cancer metastasis. Functionally, SUCLA2-associated SGs facilitate the translation of antioxidant enzymes, such as catalase, which in turn reduces oxidative stress within cancer cells and helps them evade anoikis. Clinically relevant data support this finding, showing a correlation between SUCLA2 expression, catalase levels, and the metastatic potential in lung and breast cancer patients.[131] Receptor for activated C kinase 1 (RACK1) belongs to the WD-repeat protein family and is an integral part of the ribosome structure. Upon MARylation, RACK1 plays a critical role in the assembly of SGs, fostering its colocalization with key SG components such as G3BP1 and 40S ribosomal proteins. In ovarian cancer cells, the study underscores the existence of a PARP14/TARG1-regulated RACK1 MARylation cycle that governs SG assembly and disassembly.[132] RACK1 is implicated in the progression and development of drug resistance in a variety of cancers, including oral, gastric, breast, colon, cervical, liver, and osteosarcoma.[133–135] Specifically, RACK1 modulates signaling pathways like MEK/ERK, NF-κB, induces autophagy, mediates Src-dependent tyrosine phosphorylation of Anxa2, and activates the AKT/mTOR/ASCT2 axis, which drive cancer progression.[136–138] Furthermore, it was shown that in colon cancer, Rbfox2 (Fox-1 homolog 2), induced by resveratrol treatment, dissociates from SGs to prevent cancer tissue progression.[139]

Finally, the interaction of SGs with RBPs in cancer cells can be influenced by post-translational modifications (PTM), which affect their ability to bind mRNAs and participate in granule assembly. PTMs including methylation,[54–57] poly (ADP-ribosylation) (PARylation), acetylation, ubiquitination,[9,32] SUMOylating,[59] glycosylation,[68] phosphorylation,[83] and neddylation[46,47] have been shown to influence RBPs, the key regulators in RNA dynamics, and cause various diseases including cancers. The Figure 2 presented the complex role of post-translational modifications in regulating RBPs within SGs, offering a deeper understanding of the dynamic processes that control these cellular structures.

Role of translation initiation factors in cancer and stress granules

Translation initiation factors and their involvement in SGs in relation to cancer is a multifaceted and critical area of research. Studies have revealed the pivotal role of translation initiation regulation in cellular responses to environmental and intrinsic stresses, particularly through the assembly of SGs, which modulate protein translation and influence cancer cell sensitivity to chemotherapy and survival. eIF4F complex composed of eIF4E, eIF4G, and eIF4A is a central player in cap-dependent translation initiation.[23] eIF4E, as the cap-binding protein, is central to cap-dependent translation initiation, and its interaction with eIF4G is governed by mTORC1-mediated events, particularly through the actions of 4E-BP1.[24,25] Inhibitors targeting mTORC1, such as rapamycin and its analogues, disrupt this process, reducing translation initiation and potentially sensitizing cancer cells to chemotherapy or radiation therapy.[140,141]

eIF2α is another critical translation initiation factor whose phosphorylation status impacts protein synthesis.[38] Various kinases (such as PKR, PERK, GCN2, and HRI) can phosphorylate eIF2α at serine 51 under stress conditions, leading to a global decrease in translation initiation and SG formation.[39,43,48] This event can paradoxically promote cancer cell survival by selectively translating mRNAs containing upstream open reading frames or internal ribosome entry sites. Manipulating eIF2α phosphorylation, either by activating or inhibiting the relevant kinases, can influence SG formation and thereby affect cancer cell response to treatment. For instance, PRMT7, a protein arginine methyltransferase, was discovered to methylate eIF2α, affecting its role in SG assembly and potentially influencing the cellular stress response.[142] Musashi-1 (MSI1) appears to be a key driver in orchestrating the formation of SGs through its interaction with the PKR/eIF2α signaling pathway. In the development of medulloblastoma, the balance between pro-survival and pro-death signals was orchestrated by the integrated stress response (ISR) pathway, especially through the regulation of eIF2α phosphorylation and subsequent SG formation.[143] DNA damage-inducible protein 34 (GADD34) acts as a regulatory subunit for PP1, guiding it specifically to the phosphorylated eIF2α molecule. PP1/GADD34 complex effectively reverses the stress-induced eIF2α phosphorylation, enabling the resumption of regular protein synthesis and dissolving SGs.[144]

The transcription factor PURα has been found to engage with translation initiation factors like PABPC1, eIF3B, and eIF3F in the cytoplasm, impacting mRNA translation, specifically by interacting with the 3′-untranslated region (3′UTR) of IGFBP3 mRNA to repress its translation initiation, thereby promoting esophageal squamous cell carcinoma progression.[145] In pancreatic ductal adenocarcinoma cells, SUMOylation of eIF5A has been shown to modulate its activities and influence stress responses, as well as SG formation under heat shock stress. Changes in

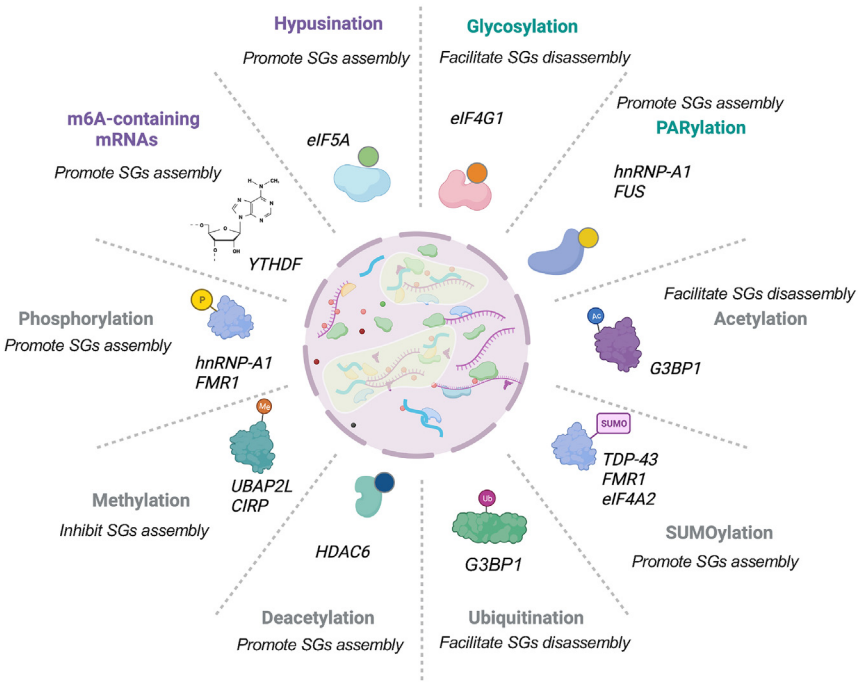

Figure 2. Post-translational modifications of RNA-binding proteins in SGs

Various posttranslational modifications, including phosphorylation, acetylation, ubiquitination, hypusination, glycosylation, ubiquitination, methylation, and SUMOylation, can significantly alter the function, localization, and interaction of RBPs, thereby influencing SG assembly, maintenance, and disassembly.

eIF5A SUMOylation status have also been linked to alterations in the stability and trafficking of the protein, affecting its overall contribution to cellular homeostasis and stress resilience.[146] Conclusively, translation initiation factors are central to the control of gene expression at the level of protein synthesis, which also play a critical role in the formation and dynamics of SGs, sustaining cancer cell viability and determining responsiveness to therapy.

Indeed, it is crucial to acknowledge that the multifaceted roles of various factors implicated in SG dynamics extend beyond their involvement in SGs. In the context of cancer, SG factors often participate in a myriad of pathways that govern fundamental processes such as cell proliferation, survival, metastasis, and therapy resistance. For instance, TIA-1 and G3BP, which are integral to SG formation, also have critical roles in mRNA processing, transport, and stability, all of which are perturbed in cancer.[147,148] Translation initiation factors like eIF4F components are similarly implicated in oncogenic signaling, where dysregulation can lead to uncontrolled protein synthesis favoring tumor growth.[149,150] This generalization ensures a balanced perspective on the extensive influence of SG-related proteins in cancer beyond their role in SG dynamics.

Stress granules and dysregulated cellular signaling

The dysregulation of cellular signaling and its intricate interplay with SGs form a compelling narrative in the context of cancer progression. Certain oncogenes and tumor suppressor genes have been shown to influence SG dynamics, affecting their formation, composition, and disassembly. Mutations in these genes can alter how SGs regulate signaling pathways in cancer cells, impacting cellular responses to stress and therapy.

Mammalian target of rapamycin complex 1 (mTORC1) is a crucial regulator of cellular growth, proliferation, metabolism, and survival, and its abnormal activity is often closely related to the occurrence and development of tumors.[151,152] The relationship between SG formation and mechanistic mTORC1 activity is complex and multifaceted.[41,153] On one hand, mTORC1 signaling normally stimulates protein synthesis but is also implicated in the establishment and maintenance of SGs. Many tumor characteristics require mTORC1 activity, but mTORC1 overactivation ultimately sensitizes cells to apoptosis.[10] Therefore, mTORC1 activity in cancer cells needs to be balanced. mTORC1's phosphorylation of eukaryotic translation initiation factor releases 4E-BP1 from eIF4E, allowing eIF4E to associate with eIF4G and contribute to SG assembly under mild stress conditions. Additionally, mTORC1-dependent S6 kinases 1 and 2 (S6K1 and S6K2) can directly or indirectly regulate SG assembly and persistence.[153] Under certain conditions, components of mTORC1 can become sequestered within SGs, resulting in a decrease in its overall activity. This means that when cells experience stress, mTORC1's constituent parts can transiently localize to these cytoplasmic condensates, effectively pausing their participation in the active complex and thereby attenuating the signaling cascade governed by mTORC1, which is crucial for controlling cellular growth, metabolism, and protein synthesis. During recovery periods, SG disassembly relies on the activity of proteins like DYRK3, a dual specificity kinase, which can activate mTORC1 by phosphorylating and dissociating PRAS40 from

mTORC1.[49] Meanwhile, DYRK3 forms a complex with G3BP2, which collaboratively facilitates the localization of lysosomal-TSC2, ultimately suppressing mTORC1 activity, particularly under conditions of low lactate stress where ETV4 is involved in regulation.[154] The protein astrin plays a pivotal role in modulating cellular responses to stress by influencing the interaction between mTORC1 and its core component raptor, as well as the recruitment and release of raptor from SGs, thereby adjusting the activation state of mTORC1. When cells encounter stressors such as oxidative stress, astrin can facilitate the dissociation of raptor from the mTORC1 complex and redirect it toward association with SGs.[10]

mTORC1 is also involved in the disassembly of SGs, and Hsp90 promotes translation recovery by reactivating two translation regulatory kinases, DYRK3 and mTORC1, which are gradually released from disassembled SGs.[50] B7-H3 is an immune checkpoint molecule whose elevated expression is commonly associated with immune evasion in tumors. Functioning as a central hub for cellular signaling in response to nutrient and energy status, mTORC1 activates its downstream effector, p70 S6 kinase, to modify YY2 through phosphorylation. This phosphorylation event alters YY2's activity or stability, culminating in increased expression of the B7-H3 gene.[155] Thus, mTORC1 indirectly facilitates tumor cells' escape from immune surveillance and attack by this mechanism. In summary, there exists a bidirectional regulatory interaction between SG formation and mTORC1 activity, reflecting the intricate mechanisms by which cells fine-tune translation and mount adaptive responses to stress.

Wnt signaling pathway is a vital cell-to-cell communication mechanism involved in development, differentiation, regeneration, and the initiation and progression of various cancers.[156] The Wnt signaling pathway is interconnected with SGs in several aspects. Studies have demonstrated that Disheveled (Dvl), a key effector in the Wnt signaling pathway, negatively regulates SG assembly. Specifically, overexpression of Dvl2, an isoform of Dvl, interferes with SG formation through its DEP domain. Dvl2 engages with G3BP, a downstream component of the Ras signaling pathway that participates in SG assembly, and manipulates SG formation through a mechanism involving Rac1-mediated suppression of RhoA activity.[157] Additionally, the Wnt pathway can influence SG function and cell fate determination through interactions with Rack1 and activation of the JNK signaling pathway.[158]

p53 signaling and SGs are intricately interconnected in cancer, playing pivotal roles in cellular responses to environmental pressures, maintenance of genomic stability, and determination of cell fate. Multiple studies have highlighted that p53 mRNA itself participates SG formation, such as during B lymphocyte activation, where p53 mRNA is incorporated into SGs for translational repression or storage, thereby regulating p53 protein levels.[73] Key regulators like TIA1 are involved in controlling the localization and translation of p53 mRNA, engaging with specific sequences in p53 mRNA to regulate its accumulation and release from SGs during periods of cellular stress.[159] In breast cancer and non-small cell lung cancer, the normal functioning of the p53 signaling pathway is influenced by SG-associated proteins like G3BP2 and USP10. G3BP2 interacts with USP10 to indirectly suppress p53 signaling, as USP10 stabilizes G3BP2 expression and facilitates the cytoplasmic shift of p53 from the nucleus, attenuating p53's transcriptional activity.[73] In prostate cancer, USP10's interaction with G3BP2 also influences p53 activity through the modulation of p53 ubiquitination, contributing to poor clinical outcomes.[75,114] Actually, the interplay between the p53 signaling pathway and SGs extends across various cancer types, where it influences the spatiotemporal distribution and functional activity of p53 through a series of intricate regulatory mechanisms.

Stress granules and cancer-related genetic mutations

Genetic mutations can also affect the formation of SGs, thereby affecting the effectiveness of cancer treatment and tumor progression. Mutant KRAS, especially prevalent hotspot mutations such as KRAS G12 and G13 in various human malignancies, acts as a prominent oncogenic driver.[160,161] Research demonstrates that mutant KRAS regulates prostaglandin metabolism, particularly by enhancing the expression of cyclooxygenase-2 (COX-2) and decreasing the degradation of 15-deoxy-Δ12,14-prostaglandin J2 (15-d-PGJ2). This secreted signaling lipid molecule, 15-d-PGJ2, promotes and sustains the formation of SGs within cells, thereby conferring resistance to a variety of stress stimuli and chemotherapeutic drugs. Additionally, mutant KRAS impacts the formation and dissolution of SGs through modulation of signaling pathways like RAF-MEK-ERK and PI3K-AKT-mTORC1. By inhibiting the synthesis of 15-d-PGJ2 or its interaction with target proteins within these cancer cells, it might be possible to sensitize mutant KRAS tumor cells to chemotherapy, leading to improved treatment response and potentially better clinical outcomes for patients with mutant KRAS-driven cancers.[7]

U2AF1 is a crucial RNA splicing factor that plays a pivotal role in recognizing the 3′ splice site (30SS) in the splicing process.[162] Mutations in U2AF1, such as S34F and Q157R, introduce novel RNA-binding events at specific positions near the 30SS, resulting in aberrant splicing outcomes.[163] Mutations in U2AF1 are associated with altered behavior of SGs in a multifaceted manner involving RNA binding and splicing. It is demonstrated that in myeloid malignancies such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), cells with U2AF1 mutations show a heightened SG response to oxidative stress.[164] The accumulation of SGs in these cells implies a greater propensity to cope with detrimental conditions possibly through aggregating stress-responsive mRNAs and proteins, thereby fostering survival and proliferation under stressful conditions. Treatment with compounds like ISRIB, an integrated stress response (ISR) inhibitor, reverses the survival advantage conferred by increased SG formation in U2AF1 mutant cells, underscoring the importance of SG dynamics in cancer progression driven by U2AF1 mutations.[165] This finding emphasizes the potential of targeting SG dynamics as a novel therapeutic strategy for cancers driven by U2AF1 mutations.

SPOP (Speckle-type POZ protein) mutations are implicated in the relationship between cancer and SGs. SPOP, in its wild-type form, serves as a substrate-binding subunit of an E3 ubiquitin ligase complex that orchestrates the ubiquitin-dependent degradation of key targets such as Caprin1, thus regulating the assembly and disassembly of SGs. In prostate cancer cells harboring SPOP mutations, the augmented formation

of SGs mediated by Caprin1 contributes to the survival of cells under hostile conditions and can increase tumor invasiveness and chemoresistance to therapies such as docetaxel.[166]

Stress granules and cancer cell senescence

Cellular senescence appears to have a complex relationship with SG formation. On one hand, senescence negatively impacts SG assembly through changes in the phosphorylation state of eIF2α due to the loss of CReP, which is a negative regulator of eIF2α phosphorylation. Additionally, senescent cells downregulate G3BP1 and TIA-1/TIAR, two key SG-nucleating proteins, by decreasing the levels of Sp1, a transcription factor that influences their expression.[167] On the other hand, senescent cells appear to exploit SGs under acute stress to maintain their viability. They actively recruit p21 mRNA and its activating factor CUGBP to SGs, which seems to bolster their resistance against entering a permanent growth arrest state.[168] Moreover, SGs in tumor cells can secrete PAI-1, which exerts a paracrine effect on the surrounding microenvironment, countering senescence in neighboring cells.[169]

Despite the decreased proliferative capacity of senescent cells, SGs also play a role in shielding these cells from apoptosis. During periods of stress, SGs can accumulate pro-apoptotic factors, effectively buffering them from triggering cell death pathways. In particular, they may hinder apoptosis by interfering with mTORC1 signaling, which is a key regulator of cellular metabolism and survival.[29,34,153] However, intriguingly, fully senescent cells do not seem to display an increase in SG formation under stress, contrasting with what might be expected from pro-senescent cells. These findings highlight the intricate and dual nature of SGs in the context of cellular senescence and cancer, where they can both contribute to the maintenance of cellular homeostasis and the persistence of senescent cells, including those in a cancerous milieu.

Stress granules and cancer cell death

Research indicates that altering the balance of SGs, either by facilitating their formation or by impeding their breakdown, can promote the demise of cancer cells. SGs serve as a protective mechanism against the hyperactivation of MAPK signaling by encapsulating proteins such as PKC/Pck2.[158] Furthermore, the DEAD-box RNA helicase DDX3X plays a role in bolstering the survival of cancer cells through its interactions with SGs.[170] By encasing elements like RACK1, SGs can thwart the activation of the NLRP3 inflammasome and prevent apoptosis in cancer cells.[171]

A recent study by Fujikawa et al. has shed light on a novel mechanism through which SGs contribute to the inhibition of stress-induced apoptosis in cancer cells. The researchers employed proteomic analyses to identify previously unknown components of SGs and discovered that executioner caspases, specifically caspase-3 and -7, are selectively sequestered into these granules. The accumulation of caspase-3 and -7 within SGs effectively inhibits their enzymatic activities, thereby suppressing apoptosis triggered by different stress factors. By averting apoptosis, SG-mediated sequestration of executioner caspases facilitates cancer cells' survival in stressful tumor microenvironments, promoting tumor growth and progression[172] Additionally, SGs are capable of influencing cell destiny by vying with pathways that lead to cell death. The introduction of glucocorticoids has been noted to increase the formation of SGs, subsequently disrupting SG dynamics and making cancer cells more susceptible to death induced by chemotherapy. Conversely, cancer cells can utilize SGs for their survival by swiftly resolving them, for instance, through the upregulation of HSP70 expression, which dissolves SGs, enabling cancer cells to adjust to low oxygen conditions. Under stress, eIF4GI recruits TRAF2 to SGs, curtailing TNFR1 activity. TRAF2 is crucial for signaling TNF-α to activate nuclear factor κB (NF-κB), culminating in cell death.[173] Additionally, SG components, via DDX3X, engage with NLRP3 to trigger the inflammasome, facilitating the release of IL-1β and IL-18 that support cell death.[174] Concurrently, the assembly of SGs entraps DDX3X, obstructing the NLRP3 inflammasome and safeguarding macrophages against apoptosis. In oral cancer research, the generation of SGs in M2 tumor-associated macrophages has been shown to induce the secretion of CCL13, thus fueling the malignant progression of cancer cells.[175]

Stress granules in cancer metabolic reprogramming

Metabolic reprogramming in cancer cells includes enhanced glycolysis, altered lipid metabolism, and amino acid metabolism adjustments to support rapid tumor growth and resist adverse conditions such as hypoxia and nutrient deprivation. SGs have been shown to affect mitochondrial function indirectly by regulating the translation of proteins involved in mitochondrial dynamics and the tricarboxylic acid (TCA) cycle. Aside from glutamine replenishing the TCA cycle, colon cancer cells promote SG assembly by producing complex glutaminase GLS1 as well as CAPRIN1 dimers under glutamine deprivation.[176] Furthermore, in the glycolysis pathway of cancer cells, fructose-1,6-bisphosphate (F1,6BP) has the ability to enhance the breakdown of SG.[177] Within cancer, SG plays a crucial role in the abnormal alteration of fatty acid metabolism via mitochondria. Through mitochondrial voltage-dependent anion channels (VDAC), SG prevents fatty acids from entering mitochondria during nutrient deprivation, thereby reducing fatty acid oxidation. In obesity-related pancreatic ductal adenocarcinoma, this process reduces oxidative damage and preserves fatty acids.[178]

Key component of SGs as G3BP1 engages with multiple signaling pathways, including the Wnt, TGF-β/Smad, and PI3K/Akt/mTORC1.[63,64,72] These signaling cascades are fundamental to the proliferation, invasion, and metastasis of tumor cells, highlighting G3BP1's integral participation in the deregulated metabolism that supports cancer progression. Another study highlighted the role of G3BP1 in modulating the expression of G3BP2 and the involvement of post-translational modifications such as arginine methylation on G3BP2 at residue R468 by PRMT5. This modification was shown to stabilize G3BP2, which in turn activated the transcription of genes involved in *de novo* lipogenesis, including acetyl-CoA carboxylase (ACLY) and fatty acid synthase (FASN). This activation was coupled with the enhancement of lipid metabolism and tumorigenesis in head and neck squamous cell carcinoma.[179] In prostate cancer, research has revealed that G3BP1 interacts with USP7 and PRMT5, contributing to the stabilization of G3BP2 and influencing its ubiquitination status.[180] This

in turn affects the functionality of deacetylase SIRT1, ultimately impacting the activity of downstream transcription factors like NF-κB and β-catenin, culminating in an increase in *de novo* lipid synthesis, thus enhancing the malignancy and drug resistance of the tumor.

Stress granules and therapy resistance in cancer

SGs indeed play a role in conferring therapeutic resistance in cancer cells by serving as a protective mechanism against the cytotoxic actions of anti-cancer therapies. Actually, SGs can shield cancer cells from the lethal effects of chemotherapy, radiotherapy, and other therapeutic interventions through several mechanisms. Firstly, SGs help cancer cells survive under the stress conditions induced by chemotherapy or radiation therapy by preventing global protein synthesis. This mechanism reduces therapy-induced protein damage, allowing cells to repair DNA damage and restore normal functions. Secondly, under the protection of SGs, certain key stress-responsive and pro-survival mRNAs are preferentially translated, such as anti-apoptotic proteins and components of cell survival signaling pathways. This aids cancer cells in resisting therapy-induced cell death. Thirdly, SGs can foster therapy resistance by influencing cell-cycle arrest, enhancing DNA damage repair mechanisms, and activating cell survival signaling pathways. Lastly, SGs can recruit a variety of signaling molecules, including proteins involved in the regulation of cell survival and apoptosis. The local accumulation and interaction of these molecules may further enhance the survival capabilities and therapeutic resistance of cancer cells.

Stress granules and cancer immune evasion

Immunotherapy has become the fourth major cancer treatment method following surgery, chemotherapy, and radiation therapy, demonstrating significant therapeutic effects on certain types of cancer. However, immune therapy resistance is a critical issue that arises when cancer cells develop tactics to avoid detection and elimination by the immune system.[181]

SGs have been implicated in the regulation of cell survival, adaptation to adverse microenvironments, and evasion of both intrinsic cell death programs and immune surveillance. The connection between SGs and cancer immune evasion occurs through several mechanisms. Firstly, SGs can influence the immune response by regulating the translation of interferons and cytokines, which are critical for triggering and maintaining the inflammatory response to cancer cells. Research findings suggest that G3BP2 is intricately linked to the regulation of PD-L1. Under stress, G3BP2 stabilizes PD-L1 mRNA and ultimately leads to elevated PD-L1 protein expression. Pharmacological inhibition of G3BP2 using compounds like C108 has been shown to reduce PD-L1 expression both *in vitro* and in mouse models of cancer.[182] This reduction in PD-L1 leads to increased infiltration of immune cells into tumors and improved survival outcomes in experimental settings. Other factors involved in SG also regulated PD-L1 transcription and stability. The research by Coelho et al. revealed that oncogenic RAS, through the mitogen-activated protein kinase (MEK) signaling cascade, decreases TTP function, leading to stabilization of PD-L1 mRNA and enhanced PD-L1 protein expression. This mechanism contributes to the ability of cancer cells to resist immune attack.[183] TTP acted as a direct regulator of PD-L1 expression. Under the influence of doxorubicin, TTP expression in cancer cells was elevated, which correlated with a decline in PD-L1 mRNA and protein expression.[184] The link between the regulation of immune checkpoint expression and SGs has been reported in other studies. The ROQUIN family proteins, especially Roquin, regulate immune checkpoint expression by functioning in SGs and controlling the fate of mRNAs encoding immune-related proteins. Notably, Roquin forms part of a multi-protein complex within SGs, associated with mRNA decay factors like Rck and Edc4. These complexes are involved in mRNA decapping, a process that destabilizes mRNAs by removing the protective 5′cap, leading to their degradation. Specifically, Roquin has been demonstrated to repress inducible costimulator (ICOS) mRNA through the miRNA machinery in T cells, which is crucial for T cell activation, preventing excessive immune responses and autoimmunity. Failure of Roquin to properly regulate ICOS mRNA contributes to autoimmune lymphoproliferation, as seen in sanroque mice that carry a mutation in Roquin (M199R).[185–187] Microtubules and their associated molecular motor kinesin 1 are crucial for the proper assembly, transport, and disassembly of SGs to permit translation. Importantly, PD-1 mRNA translation requires microtubule-dependent SG dynamics. Thus, microtubule-driven SG dynamics are integral to post-transcriptional control of inhibitory immune checkpoints in T cells, revealing opportunities for immunotherapy manipulation.[188] Moreover, studies have demonstrated a link between immunotherapy-induced immunogenic cell death and SGs by affecting ER stress and subsequent eIF2α phosphorylation.[189] The dynamic association between SGs and key immune checkpoint components determines the complexity of their regulation of immune responses, but at the same time, this association also reveals a potential way to improve the effectiveness of immunotherapy.

Stress granules and cancer chemotherapy resistance

The formation of SGs is thought to play a dual role in the context of chemotherapy resistance in cancer cells. Actually, several chemotherapy drugs, including bortezomib, cisplatin, and 5-fluorouracil (5-FU), have been shown to induce SG formation. Sorafenib and lapatinib, inhibitors of receptor tyrosine kinases, activate PERK and promote SG assembly.[190,191] Specifically, bortezomib, as a proteasome inhibitor, has shown efficacy in the treatment of hematological malignancies such as multiple myeloma and has also been found to strongly induce the assembly of SGs in cancer cells through promoting eIF2α phosphorylation.[192] Meanwhile, research has shown that 5-FU, a common antimetabolite chemotherapy drug, can induce SG aggregation through RNA binding.[193]

Genetic manipulation or pharmacological inhibition of SG-nucleating proteins such as G3BP1/2 and Caprin1 or inhibiting upstream signaling pathways like eIF2α phosphorylation can sensitize cancer cells to chemotherapy. Studies have revealed that under the influence of various chemotherapeutic agents such as cisplatin, paclitaxel, and fluorouracil, tumor cells employ PKR-mediated eIF2α phosphorylation and the subsequent formation of SGs as a mechanism to evade apoptosis induced by these drugs, thereby enhancing their tolerance to chemotherapy.[194] Additionally, certain chemotherapy drugs like doxorubicin, when combined with hyperthermia, are shown to induce SG

formation through a non-eIF2α-dependent pathway, further associating with the development of chemoresistance. Ataxin-2-like protein (ATXN2L) in head and neck squamous cell carcinomas (HNSCCs) promotes the stabilization of G3BP2 through interactions with USP7 and PRMT5. This stabilized G3BP2 subsequently amplifies *de novo* lipogenesis, or the generation of new lipids, by activating acetyl-CoA carboxylase.[180] Clinical studies further indicate that the protein levels of G3BP2, PRMT5, and the methylated form of G3BP2 (G3BP2-R468me2) positively correlate with poorer prognosis. Research has revealed that G3BP1 interacts with YWHAZ, jointly participating in the regulation of chemoresistance in gastric cancer.[78] Patients with gastric cancer expressing higher levels of G3BP1 and YWHAZ tend to have poorer survival outcomes following adjuvant chemotherapy, suggesting that the expression of these proteins could serve as predictive biomarkers for the efficacy of adjuvant chemotherapy in gastric cancer patients. Research has demonstrated that the administration of recombinant human MG53, a member of the TRIM protein family, can effectively decrease the activity of G3BP2 in non-small cell lung cancer cells.[195] This reduction in G3BP2 activity has been correlated with the attenuation of SG formation, which is often implicated in promoting resistance to chemotherapeutic agents like cisplatin. In prostate cancer, overexpression of Caprin1 promotes the formation of SGs, and this augmented stress response aids in the survival of cells under adverse conditions like those induced by chemotherapy drugs such as docetaxel. Prostate cancer cells harboring SPOP mutations display increased resistance to docetaxel and other stress-inducing agents, potentially due to the aberrant activation of SG assembly pathway mediated by Caprin1.[166]

Overexpression of certain SG components, like mutant forms of KRAS, has been associated with increased SG formation and enhanced chemoresistance in cancer cells.[7] Mutant KRAS can increase the production and secretion of 15-d-PGJ2, which can then act in an autocrine or paracrine manner to promote SG assembly, protecting cells from the cytotoxic effects of chemotherapy and radiation.[7] In breast cancer, CUGBP1 is associated with SGs and impacts the chemoresistance of cells to chemotherapy drugs by regulating the translation of p21 mRNA.[196] Other studies have shown that selenite compounds, such as sodium selenite, can induce the assembly of SGs by affecting the translation initiation mediated by 4EBP1, which in turn may influence the efficacy of chemotherapy drugs.[42] Concurrently, SGs reciprocally impact the effectiveness of chemotherapy agents by sequestering key proteins like RACK1, thereby suppressing apoptotic signaling pathways and contributing to chemotherapy resistance. Expression of long interspersed element-1(LINE-1) and activity are tightly controlled in healthy differentiated somatic cells but can be abnormally activated in tumor cells. Research has shown that chemotherapy agents like paclitaxel can induce the formation of SGs, which in turn recruit and stabilize LINE-1 mRNA.[197]

Circadian rhythm regulators, such as brain and muscle ARNT-like protein 1 (BMAL1), also play a role in the assembly of SGs and may influence the sensitivity of cancer cells to chemotherapy. Disruptions in the circadian rhythm, especially the rhythmic expression of EIF2α, can impact the formation of SGs and may affect the optimal timing for administering chemotherapy drugs.[198] Thus, understanding how circadian rhythms interact with SGs and chemotherapy effectiveness could guide scientists in optimizing the timing of chemotherapy administration to align with the patient's internal biological clock, potentially enhancing treatment efficacy and minimizing side effects. RNA modification is also one of the causes of chemotherapy resistance. For example, studies have revealed that N7-methylguanosine (m7G) modification enables m7G internal mRNA to be selectively recognized by Quaking protein (QKI).[199] QKI7 interacts with G3BP1 through the C terminus and transports internal m7G-modified transcripts into SG, weakening the translation efficiency of essential genes in the Hippo signaling pathway, thereby sensitizing cancer cells to chemotherapy. Most of the effects of SG on tumor chemotherapy are negative. But not all products of stress lead to this couple. For example, studies have shown that after stress strongly induces host cells to produce endogenous Z-RNA, Z-RNA will be localized to SG, and finally, ZBP1-driven necroptosis significantly promotes tumor chemotherapy.[200]

Stress granules and cancer radiotherapy resistance

SGs can play a pivotal role in mediating resistance to cancer radiotherapy. Upon exposure to ionizing radiation, SGs dynamically orchestrate the sequestration and translational control of vital transcription factor mRNAs, such as hypoxia-inducible factor-1 (HIF-1). HIF-1 is notably upregulated during hypoxia and governs the expression of numerous genes involved in cellular survival strategies and adaptation to oxygen-deprived microenvironments. Therefore, SGs effectively preserve these transcripts ready for rapid and efficient translation post-stress, thereby enabling cancer cells to recover swiftly and mend the harm caused by radiation insults.[201] Experimental evidence shows that the inhibition of G3BP1 can render lung cancer cells more susceptible to radiation, thus underscoring the involvement of SGs in radiotherapy resistance.[22] This intricate relationship between SGs and various cancer treatment modalities emphasizes the need for a nuanced understanding to optimize therapeutic interventions. As summarized in Figure 3, it illustrates the diverse functions of SGs in cancer cells, emphasizing their significant roles in cancer progression and various cancer treatment resistance.

Targeting stress granules in cancer treatment

Researchers are exploring ways to target SGs to improve cancer treatment outcomes. Some drugs can potentially promote the formation of SGs, thereby enhancing drug resistance in tumor cells, whereas others might work by inhibiting SG assembly or disassembly and boosting the effectiveness of anticancer treatments. Therefore, targeting SGs as a central strategy in cancer therapy involves the identification of suitable drug combinations or therapeutic windows to optimize efficacy and minimize adverse effects.

Small molecules and compounds have been identified that can interfere with SG formation or components, leading to enhanced sensitivity to chemotherapeutic agents. Small molecule inhibitors specifically designed to target G3BP have been developed and studied to modulate the formation of SGs.[202] For instance, compounds referred to as G3BP inhibitors (such as G3BP inhibitor a, G3Ia, and G3BP inhibitor b, G3Ib) have been synthesized to bind selectively to specific pockets within G3BP1/2 proteins, thereby influencing G3BP-mediated SG aggregation and enabling the prevention or dissolution of SGs. One study reported on a small molecule, Ceapin-A7, which was able to inhibit SG

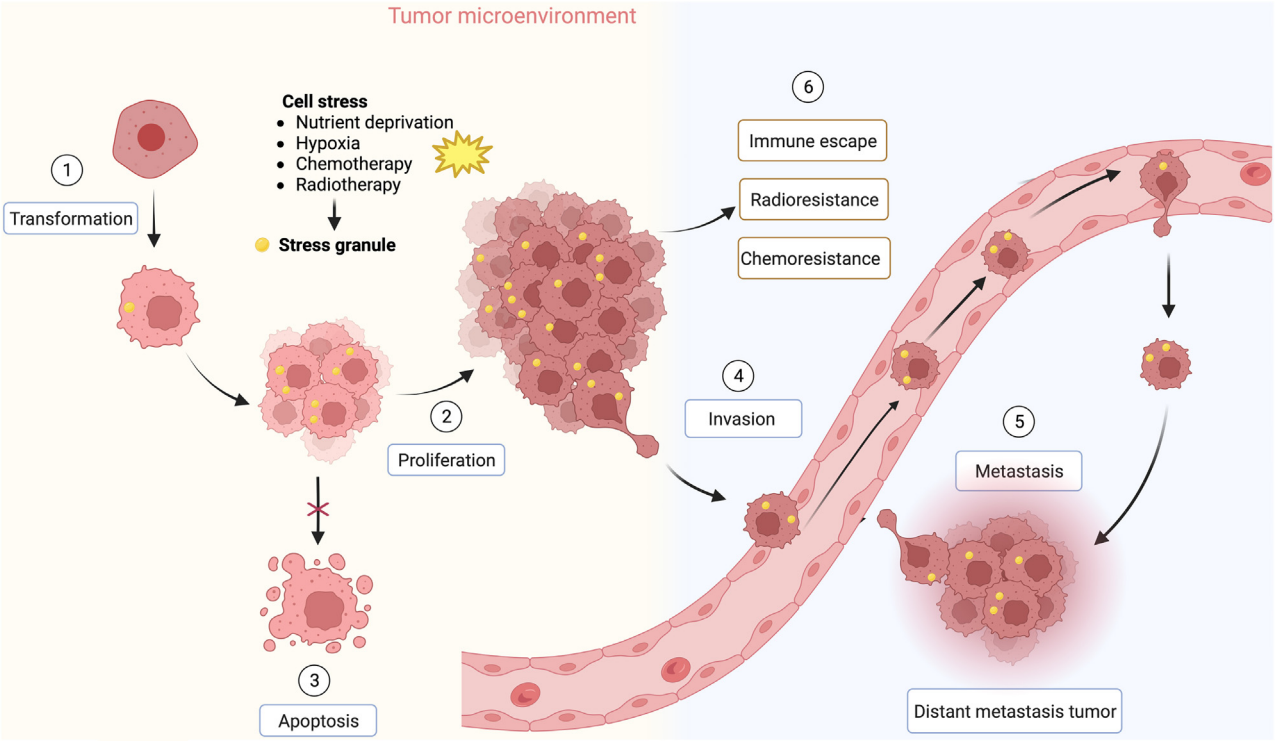

Figure 3. SGs play multifaceted roles that contribute to tumor progression, cell survival, and resistance to therapies

Stress granules within cancer cells assume a complex array of roles that bolster tumor progression, enhance cell survival, and foster resistance to various therapeutic interventions. Stress granules enable cancer cells to adapt to unfavorable conditions such as hypoxia, nutrient scarcity, and exposure to chemotherapeutic agents or radiation, thereby promoting a more aggressive and treatment-resistant tumor phenotype.

formation by targeting the G3BP1-RNA interaction, thereby sensitizing glioblastoma cells to chemotherapy.[203] Additionally, research has revealed that USP7 contributes to the stabilization of G3BP2 protein, preventing its degradation and consequently driving *de novo* lipogenesis and tumorigenesis in head and neck squamous cell carcinoma.[154] By targeting USP7 with inhibitors, such as P5091, researchers aim to destabilize G3BP2 and potentially develop a new therapeutic approach.[204]

An eIF2α dephosphorylation inhibitor Salubrinal increases SG formation and can sensitize cancer cells to chemotherapy.[205] Targeting SGs through Salubrinal can render cancer cells more sensitive to the killing effects of chemotherapeutic drugs, thereby improving the effectiveness of the treatment. Actually, studies have shown that Salubrinal treatment can indeed sensitize certain cancer cells to chemotherapeutic agents like bortezomib, cisplatin, or etoposide by modulating the stress response pathway and influencing cell fate decisions toward apoptosis.[206] ISRIB (integrated stress response inhibitor) is a significant small molecule drug that can interfere with the phosphorylation of the key protein eIF2α during the stress response and its interaction with the eIF2B complex, thereby inhibiting the formation of SGs.[207] The HuR inhibitor MS-444 is a compound isolated from microbial sources that works by interfering with the homodimerization of HuR (human antigen R). By inhibiting HuR's ability to form dimers, MS-444 effectively hinders its cytoplasmic export, leading to decreased stability of HuR-bound mRNAs. It has been shown to reduce colorectal and pancreatic tumor growth and sensitize cancer cells to apoptotic stimuli and chemotherapy agents.[208,209] Several successful anticancer chemotherapy drugs, such as mitoxantrone (a prototype immunogenic-cell-death-inducing anthracycline), have the property of inducing immunogenic cell death, thereby inducing an anticancer immune response.

Rosuvastatin, a widely prescribed cholesterol-lowering medication belonging to the class of HMG-CoA reductase inhibitors, commonly known as statins, is primarily used in the management of cardiovascular risks and hypercholesterolemia.[210] Research has indicated that rosuvastatin may potentially influence the assembly and disassembly of SGs through ameliorating oxidative stress conditions, affecting microtubule dynamics within cells, or through as yet incompletely understood pathways.[211] This finding carries significance in terms of understanding how stress responses impact cellular fate and in exploring potential novel applications of statins, such as rosuvastatin, in cancer treatment or the prevention and management of other diseases related to stress responses.

Selenium-methylselenocysteine (also known as selenomethionine or selenite) is an organic selenium compound that acts as a source of dietary selenium intake for humans. Selenite can induce an elevation in oxidative stress levels within cells, which in turn can activate cellular defense mechanisms, among which is the formation of SGs.[42] By altering SG formation, selenite might sensitize cancer cells to chemotherapeutic agents or mitigate chemoresistance. This could potentially occur through mechanisms such as disrupting the stress-induced

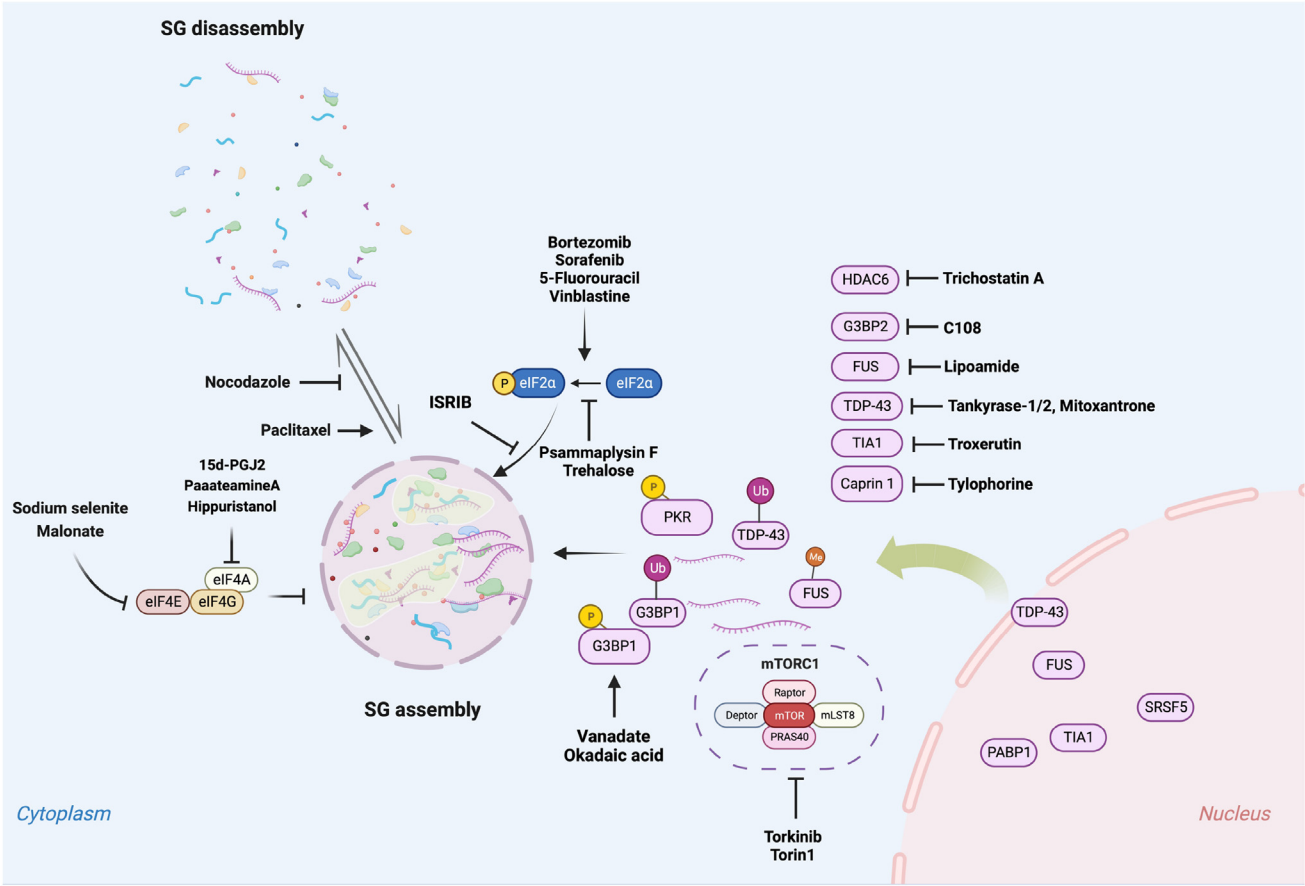

Figure 4. Compounds targeting SG formation with small molecules or compounds

This figure provides an overview of potential interventions and considerations for leveraging SGs as therapeutic targets in cancer treatment. This strategy holds promise for enhancing the effectiveness of existing cancer treatments by preventing cancer cells from using SGs as a shield against therapeutic agents.

pathways that cancer cells utilize to evade apoptosis or by influencing the translational landscape to favor pro-death protein synthesis over pro-survival ones.

circRNA-CREIT plays a role in diminishing the formation of SGs in TNBC.[11] circRNA-CREIT serves as a scaffold to facilitate the binding of PKR with HACE1, which in turn leads to the enhanced ubiquitination of PKR, particularly through K48-linked chains. Since PKR is known to phosphorylate the eIF2α, a key step in SG assembly, the downregulation of PKR by circRNA-CREIT ultimately attenuates the phosphorylation of eIF2α and consequently suppresses SG formation, affecting TNBC cells' sensitivity to chemotherapeutic agents. Figure 4 elucidates strategies and potential targets for therapeutic intervention aimed at SGs in the context of human tumors, offering insights into innovative approaches for cancer treatment. More detailed information of compounds targeting SGs is summarized in Table 2. Due to the complexity and fluidity of protein-RNA interactions in SGs themselves, potential off-target effects are a significant concern when developing inhibitors targeting SG components or their regulators. SGs are involved in a wide range of cellular processes, including metabolism, stress signaling, and cell fate decisions like apoptosis and senescence. Therefore, interventions aimed at modulating SG dynamics could inadvertently impact these processes, leading to unintended consequences or toxicity in non-cancerous cells. Moreover, achieving the balance between therapeutic benefit and maintaining necessary cellular stress responses is a delicate task. SGs have a fundamental function in the physiological stress response of healthy cells. Therefore, inhibiting SG formation or function must be done in a way that selectively targets cancer cells without compromising the ability of normal cells to cope with stress. Research on related molecular inhibitor treatments still needs to be further explored to clarify the molecular mechanism of treatment and its efficacy.

Combinations of traditional chemotherapeutics with SG-targeting agents have demonstrated synergistic effects. For instance, the use of the autophagy inhibitor chloroquine or hydroxychloroquine in conjunction with chemotherapies has shown some success in preclinical models by blocking SG formation and promoting cell death.[212] Raloxifene, a selective estrogen receptor modulator (SERM), has been demonstrated to inhibit the disassembly of SGs induced by hypoxia and, when used alongside chemotherapeutic drugs such as vinorelbine, can potentiate cancer cell death.[213] By regulating the formation and dissolution of SGs, raloxifene and similar compounds could augment the effectiveness of chemotherapy, suggesting a potential synergistic therapeutic approach.

Table 2. Compounds targeting stress granules for human tumors

Strategies	Target	Known impact on SGs	Anticancer effect	Cell lines/Patient tissue/ Murine mode	Clinical trial
Malonate	*eIF4E*	Induces SG aggregation through 4E-BP1-mediated inactivation of the eIF4E pathway	Inhibits apoptosis in HeLa cells	Human cell lines	/
Selenium	*eIF4F*	Destroys the eIF4F complex via dephosphorylation of 4E-BP1	Promotes production of ROS for targeting tumor cells	Human cell lines and mouse model	Stage I/II
15-deoxy-delta12,14-prostaglandin J2 (15d-PGJ2)	*eIF4A*	Block translation by targeting cysteine 264 and inactivating eIF4A	Antineoplastic activity	Human cell lines and human tissues	/
Hippuristanol and silvestrol	*eIF4F*	Induces SG assembly by perturbing eIF4F ATPase, helicase and RNA-binding activities	Anti-tumor and antiviral replication activity	Human cell lines	Stage I/II
Vinorelbine, vinblastine, and vincristine	*eIF2α*	Inactivating 4EBP1 or inhibiting eIF2α phosphorylation	Decrease cancer cell viability and promote apoptosis	Human cell lines, mouse model, and human tissues	Stage IV
Psammaplysin F	*eIF2α*	Decreases eIF2α phosphorylation	Increases the efficacy of bortezomib and sorafenib	Human cell lines	/
ISRIB	*eIF2B*	Reverses the effect of eIF2α phosphorylation and restores translation by targeting eIF2B and prevent the formation of SGs	Inhibits SIN-1-induced SG assembly in U2OS cells	Human cell lines	/
Pateamine A	*eIF4FA*	Activates helicase and ATPase activity of eIF4A; inhibits the binding of eIF4A to eIF4G;	Inhibits cancer cell proliferation, being less cytotoxic to non-proliferative fibroblasts	Human cell lines	/
Westeros	*eIF4A*	Stimulates the RNA-binding and helicase activity of eIF4A, resulting in the isolation of eIF4A from the eIF4F complex, and induces SG assembly	Potent inhibitor of cancer cell proliferation and tumor growth in breast, prostate, and hepatocellular carcinoma	Human cell lines	/
Hippuristanol	*eIF4A*	Inhibits the binding of eIF4A to mRNA	Inhibits proliferation of lymphoma and T cell leukemia and reverse chemoresistance	Human cell lines and mouse model	/
4Ei-1	*eIF4E*	Inhibits eIF4E binding and mediates proteasome degradation of eIF4E	Sensitizes breast and lung cancer cells to gemcitabine; promotes apoptosis of prostate cancer cells	Human cell lines	/
MAPK interaction kinases	*eIF4E*	Inhibits phosphorylation of eIF4E	Inhibits melanoma and colon cancer progression	Human cell lines and mouse model	Stage I/II
4EGI-1	*eIF4E/eIF4G*	Blocks the binding of eIF4G to eIF4E and enhances the binding of 4E-BP1 to eIF4E	Inhibits the progression of melanoma and breast cancer	Human cell lines and mouse model	/

(*Continued on next page*)

Table 2. *Continued*

Strategies	Target	Known impact on SGs	Anticancer effect	Cell lines/Patient tissue/ Murine mode	Clinical trial
4ER1Cat	*eIF4E/eIF4G*	Blocks the binding of eIF4E to eIF4G and 4E-BP1	Enhances chemosensitivity to doxorubicin in lymphoma	Human cell lines, mouse model, and human tissues	/
Torin1	*mTOR*	Inhibits phosphorylation of 4E-BP1 and impair SG formation	Sensitizes tumor cells to apoptosis	Human cell lines, mouse model, and human tissues	/
C108, 2-hydroxy-N-[1-(2-hydroxyphenyl)ethylidene] benzohydrazide	*G3BP2*	Alleviates the function of G3BP2 and impairs SG formation	Inhibits tumor-initiating cells, affects chemosensitivity and radiosensitivity in breast cancer	Human cell lines, mouse model, and human tissues	/
Phosphatase inhibitors	*G3BP*	Increases G3BP phosphorylation level and regulates SG formation	Inhibits tumor proliferation	Human cell lines, mouse model, and human tissues	/
GAP161	*G3BPs*	Regulates Ras-GAP and G3BP interactions	Enhances the antitumor effect of cisplatin	Human cell lines and mouse model	/
Nocodazole	*Microtubule inhibitors*	Blocks eIF2α phosphorylation and inhibits SG assembly	Induces apoptosis of cancer cells	Human cell lines	/
Mitoxantrone	*Topoisomerase II inhibitor*	Inhibits TDP-43 accumulation	Approved for the treatment of acute myeloid leukemia	Human cell lines	/

Concluding remarks and future perspectives

The formation of SGs in eukaryotic cells represents a conserved response that protects cells from harmful stress conditions and possesses apparent physiological advantages. The capacity of cancer cells to adapt to a range of stressful environments within their microenvironment is a hallmark of stress adaptation in cancer. By leveraging the formation of SGs, cancer cells are able to enhance their resilience to stress. Recognizing the intricacies of cellular stress responses and the fluid nature of SGs is critical for further exploration before these findings can be effectively integrated into clinical practice.

The challenge in targeting SGs for therapeutic intervention lies in their intricate biological nature and the potential risks associated with disrupting them. Developing specific inhibitors for SGs has been problematic due to the fear of disrupting vital cellular stress responses and inadvertently triggering other compensatory mechanisms. Currently, there are no Food and Drug Administration (FDA)-approved drugs that specifically target SGs. Research has identified several compounds that show promise in experimental settings, but moving from preclinical models to actual clinical applications necessitates extensive human trials to ensure both efficacy and safety.[190] Several existing pharmacological agents can hinder SG formation, but they often operate through broad-spectrum mechanisms. For example, some drugs affect the phosphorylation state of eIF2α,[205,206] which plays a key role in protein synthesis regulation during stress response. Others modulate the mTOR signaling pathway,[152] a central regulator of cell growth and metabolism, or alter the function of specific RBPs like G3BP1, all of which can indirectly impact SG dynamics.[202]

However, these drugs do not act directly on the structural integrity of SGs themselves. To develop tools capable of identifying their SG-specific functions and roles in tumorigenesis, a deep understanding of the specific interactions or modifications that govern their ability to nucleate SGs is essential. This would allow researchers to pinpoint more selective therapeutic targets and develop novel compounds that can differentiate between pathological SG formation and normal cellular stress responses. Many chemotherapy drugs, such as paclitaxel, cisplatin, 5-fluorouracil, and bortezomib, have been found to induce the formation of SGs.[193,197,214] The enhanced assembly of SGs may promote tumor cell resistance to chemotherapy and facilitate immune evasion and radiotherapy resistance in different cancer types. Researchers have devised a novel intelligent drug delivery system utilizing hollow copper sulfide nanoparticles (HCuS NPs) modified with PEGylated pH-low insertion peptide (PEG-pHLIP) encapsulating the SG inhibitor ISRIB, creating a pH-responsive and near-infrared (NIR) light-triggered controlled system named IL@H-PP. Upon NIR irradiation, IL@H-PP executes photothermal therapy (PTT), and the light-controlled release of ISRIB effectively inhibits the formation of PTT-induced SGs, rendering tumor cells more sensitive to PTT.[215] This study therefore introduces a new paradigm for anticancer and antimetastatic treatments by combining PTT with SG inhibitors like ISRIB, leveraging the unique properties of nanomaterials to augment the efficacy of PTT through modulation of the tumor microenvironment and interference with SG dynamics. In summary, investigating the synergy between SG modulators and current cancer treatments could lead to new combination therapies that enhance the effectiveness of standard treatments while reducing side effects.

Notably, SGs are not static entities; they disassemble and reform according to the stress intensity and duration. Disassembly can be regulated by ubiquitination events, SUMOylation, and the action of chaperones such as Hsp70 and Hsp90, as well as by phase-separation-regulating factors.[50,58,59,105] The inability to properly form or dissolve SGs can lead to their pathogenic persistence in cancer, where they are linked to the accumulation of aggregated proteins and abnormal overactive or inactive signaling pathway. For instance, overexpression or deregulation of SG-nucleating proteins like TIA-1 and TIAR, or alterations in eIF2α phosphorylation status, can affect SG dynamics and impact cancer progression.[83] Oxidative stress can impair SG formation by oxidizing TIA1, making cells more vulnerable to apoptosis, suggesting that manipulation of SG dynamics could be exploited therapeutically. Future research should elucidate the precise mechanisms that dictate SG assembly and disassembly, particularly the identification of molecular markers and signaling cascades that govern the transition from SG formation to dissolution. Understanding the precise molecular mechanisms that regulate SG assembly and disassembly is pivotal for advancing our knowledge of fundamental biological processes and for developing novel interventions against cancer progression where SGs play a significant role.

SGs interact with other cellular processes, such as the unfolded protein response (UPR) in the ER and autophagy pathways.[32,53] The disruption of these interconnected stress responses through SG modulation could affect cancer cell survival and tumor growth. Understanding the interplay between SGs and other cellular compartments, such as the proteasome, lysosomes, and autophagosomes, is fundamental in elucidating how cells maintain proteostasis and clear SG constituents under stress conditions. Under stress conditions, SGs may sequester proteins that would otherwise be marked for degradation by the ubiquitin-proteasome system.[216] Conversely, proteasomal dysfunction can lead to increased SG formation due to the accumulation of misfolded proteins and RBPs that normally participate in SG dynamics. Recent evidence suggests that autophagy-mediated delivery of SGs or their components to lysosomes for degradation is a potential mechanism for clearing SGs and resolving the stress response. SGs can interact with autophagic machinery, either being engulfed by autophagosomes themselves or releasing their cargo to be processed by autophagy.[53,217]Targeting these interactions could potentially open up new avenues for therapeutic intervention in cancer progression where SG dynamics are disrupted.

Advances in technology have greatly enhanced our understanding of SGs and their complex biology. The advent of super-resolution microscopy techniques, such as STORM, PALM, and SIM, has enabled researchers to visualize SGs at nanoscale resolution, providing unprecedented detail about their structure, composition, and dynamics within living cells. Additionally, techniques like BioID, APEX, and PLEx-Seq enable the labeling and identification of proteins in close proximity to a tagged SG component, helping to build detailed maps of SG interactomes and discover previously unrecognized SG constituents.[218,219] Single-particle tracking and single-molecule Förster resonance energy transfer (smFRET) allows researchers to study SG dynamics in real time at the level of individual molecules, giving insights into the kinetics of SG assembly and disassembly.[220–223] Combining these advanced techniques can provide a multi-dimensional view of SGs, from the molecular

interactions within a single granule to their variability and function across different cells and conditions. These advanced methodologies can uncover novel SG components and interactions implicated in cancer, identify SG signatures associated with therapy resistance, and reveal targets for therapeutic intervention.

In conclusion, this discussion underscores the significance of SGs in the dynamics of cellular stress and their role in disease pathogenesis, particularly in relation to tumors. The dynamic and reversible nature of SG assembly, coupled with its adaptability to various stress conditions, positions SGs as key components in maintaining cellular homeostasis and influencing disease progression. Targeting SG-associated proteins to disrupt SG dynamics could sensitize cancer cells to treatments, potentially serving as biomarkers for cancer prognosis and treatment responses. This approach could assist in the development of personalized therapeutic strategies.

ACKNOWLEDGMENTS

Due to space limit, some of the important works in this field were not cited, and we sincerely apologize to those authors whose important studies were not summarized.

Funding: This study is supported by National Natural Science Foundation of China (No. 82000212), Natural Science Foundation of Zhejiang Province (LQ21H160022), and Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2024KY989).

AUTHOR CONTRIBUTIONS

J.L.Y., R.Y.J., Z.F.D., J.B.Z., J.R., W.J.C., Z.C., and X.C.Z. all reviewed the literature and wrote the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Ivanov, P., Kedersha, N., and Anderson, P. (2019). Stress Granules and Processing Bodies in Translational Control. Cold Spring Harbor Perspect. Biol. *11*, a032813.
2. Kedersha, N., Stoecklin, G., Ayodele, M., Yacono, P., Lykke-Andersen, J., Fritzler, M.J., Scheuner, D., Kaufman, R.J., Golan, D.E., and Anderson, P. (2005). Stress granules and processing bodies are dynamically linked sites of mRNP remodeling. J. Cell Biol. *169*, 871–884.
3. Youn, J.Y., Dunham, W.H., Hong, S.J., Knight, J.D.R., Bashkurov, M., Chen, G.I., Bagci, H., Rathod, B., MacLeod, G., Eng, S.W.M., et al. (2018). High-Density Proximity Mapping Reveals the Subcellular Organization of mRNA-Associated Granules and Bodies. Mol. Cell *69*, 517–532.e11.
4. Chen, X., and Cubillos-Ruiz, J.R. (2021). Endoplasmic reticulum stress signals in the tumour and its microenvironment. Nat. Rev. Cancer *21*, 71–88.
5. Protter, D.S.W., and Parker, R. (2016). Principles and Properties of Stress Granules. Trends Cell Biol. *26*, 668–679.
6. Lavalée, M., Curdy, N., Laurent, C., Fournié, J.-J., and Franchini, D.-M. (2021). Cancer cell adaptability: turning ribonucleoprotein granules into targets. Trends Cancer *7*, 902–915.
7. Grabocka, E., and Bar-Sagi, D. (2016). Mutant KRAS Enhances Tumor Cell Fitness by Upregulating Stress Granules. Cell *167*, 1803–1813.e12.
8. Yang, P., Mathieu, C., Kolaitis, R.M., Zhang, P., Messing, J., Yurtsever, U., Yang, Z., Wu, J., Li, Y., Pan, Q., et al. (2020). G3BP1 Is a Tunable Switch that Triggers Phase Separation to Assemble Stress Granules. Cell *181*, 325–345.e28.
9. Gwon, Y., Maxwell, B.A., Kolaitis, R.M., Zhang, P., Kim, H.J., and Taylor, J.P. (2021). Ubiquitination of G3BP1 mediates stress granule disassembly in a context-specific manner. Science *372*, eabf6548.
10. Thedieck, K., Holzwarth, B., Prentzell, M.T., Boehlke, C., Kläsener, K., Ruf, S., Sonntag, A.G., Maerz, L., Grellscheid, S.N., Kremmer, E., et al. (2013). Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in cancer cells. Cell *154*, 859–874.
11. Wang, X., Chen, T., Li, C., Li, W., Zhou, X., Li, Y., Luo, D., Zhang, N., Chen, B., Wang, L., et al. (2022). CircRNA-CREIT inhibits stress granule assembly and overcomes doxorubicin resistance in TNBC by destabilizing PKR. Hematol. Oncol. *15*, 122.
12. Zhan, Y., Wang, H., Ning, Y., Zheng, H., Liu, S., Yang, Y., Zhou, M., and Fan, S. (2020). Understanding the roles of stress granule during chemotherapy for patients with malignant tumors. Am. J. Cancer Res. *10*, 2226–2241.
13. Jain, S., Wheeler, J.R., Walters, R.W., Agrawal, A., Barsic, A., and Parker, R. (2016). ATPase-Modulated Stress Granules Contain a Diverse Proteome and Substructure. Cell *164*, 487–498.
14. Zhou, Y., Panhale, A., Shvedunova, M., Balan, M., Gomez-Auli, A., Holz, H., Seyfferth, J., Helmstädter, M., Kayser, S., Zhao, Y., et al. (2024). RNA damage compartmentalization by DHX9 stress granules. Cell *187*, 1701–1718.
15. McDonald, K.K., Aulas, A., Destroismaisons, L., Pickles, S., Beleac, E., Camu, W., Rouleau, G.A., and Vande Velde, C. (2011). TAR DNA-binding protein 43 (TDP-43) regulates stress granule dynamics via differential regulation of G3BP and TIA-1. Hum. Mol. Genet. *20*, 1400–1410.
16. Kedersha, N., Panas, M.D., Achorn, C.A., Lyons, S., Tisdale, S., Hickman, T., Thomas, M., Lieberman, J., McInerney, G.M., Ivanov, P., and Anderson, P. (2016). G3BP-Caprin1-USP10 complexes mediate stress granule condensation and associate with 40S subunits. J. Cell Biol. *212*, 845–860.
17. Song, D., Kuang, L., Yang, L., Wang, L., Li, H., Li, X., Zhu, Z., Shi, C., Zhu, H., and Gong, W. (2022). Yin and yang regulation of stress granules by Caprin-1. Proc. Natl. Acad. Sci. USA *119*, e2207975119.
18. Lee, E.K. (2012). Post-translational modifications of RNA-binding proteins and their roles in RNA granules. Curr. Protein Pept. Sci. *13*, 331–336.
19. Baymiller, M., and Moon, S.L. (2023). Stress Granules as Causes and Consequences of Translation Suppression. Antioxidants Redox Signal. *39*, 390–409.
20. Mino, T., and Takeuchi, O. (2018). Post-transcriptional regulation of immune responses by RNA binding proteins. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. *94*, 248–258.
21. Dang, Y., Kedersha, N., Low, W.K., Romo, D., Gorospe, M., Kaufman, R., Anderson, P., and Liu, J.O. (2006). Eukaryotic initiation factor 2alpha-independent pathway of stress granule induction by the natural product pateamine A. J. Biol. Chem. *281*, 32870–32878.
22. Farny, N.G., Kedersha, N.L., and Silver, P.A. (2009). Metazoan stress granule assembly is mediated by P-eIF2alpha-dependent and -independent mechanisms. RNA N. Y. N *15*, 1814–1821.
23. Villa, N., Do, A., Hershey, J.W.B., and Fraser, C.S. (2013). Human eukaryotic initiation factor 4G (eIF4G) protein binds to eIF3c, -d, and -e to promote mRNA recruitment to the ribosome. J. Biol. Chem. *288*, 32932–32940.
24. Harms, U., Andreou, A.Z., Gubaev, A., and Klostermeier, D. (2014). eIF4B, eIF4G and RNA regulate eIF4A activity in translation initiation by modulating the eIF4A conformational cycle. Nucleic Acids Res. *42*, 7911–7922.

25. Feoktistova, K., Tuvshintogs, E., Do, A., and Fraser, C.S. (2013). Human eIF4E promotes mRNA restructuring by stimulating eIF4A helicase activity. Proc. Natl. Acad. Sci. USA *110*, 13339–13344.
26. Costello, J., Castelli, L.M., Rowe, W., Kershaw, C.J., Talavera, D., Mohammad-Qureshi, S.S., Sims, P.F.G., Grant, C.M., Pavitt, G.D., Hubbard, S.J., and Ashe, M.P. (2015). Global mRNA selection mechanisms for translation initiation. Genome Biol. *16*, 10.
27. Mateju, D., Franzmann, T.M., Patel, A., Kopach, A., Boczek, E.E., Maharana, S., Lee, H.O., Carra, S., Hyman, A.A., and Alberti, S. (2017). An aberrant phase transition of stress granules triggered by misfolded protein and prevented by chaperone function. EMBO J. *36*, 1669–1687.
28. Anderson, P., and Kedersha, N. (2009). RNA granules: post-transcriptional and epigenetic modulators of gene expression. Nat. Rev. Mol. Cell Biol. *10*, 430–436.
29. Heberle, A.M., Prentzell, M.T., van Eunen, K., Bakker, B.M., Grellscheid, S.N., and Thedieck, K. (2015). Molecular mechanisms of mTOR regulation by stress. Mol. Cell. Oncol. *2*, e970489.
30. Li, W., He, P., Huang, Y., Li, Y.F., Lu, J., Li, M., Kurihara, H., Luo, Z., Meng, T., Onishi, M., et al. (2021). Selective autophagy of intracellular organelles: recent research advances. Theranostics *11*, 222–256.
31. Marcelo, A., Koppenol, R., de Almeida, L.P., Matos, C.A., and Nóbrega, C. (2021). Stress granules, RNA-binding proteins and polyglutamine diseases: too much aggregation? Cell Death Dis. *12*, 592.
32. Yang, C., Wang, Z., Kang, Y., Yi, Q., Wang, T., Bai, Y., and Liu, Y. (2023). Stress granule homeostasis is modulated by TRIM21-mediated ubiquitination of G3BP1 and autophagy-dependent elimination of stress granules. Autophagy *19*, 1934–1951.
33. Bussi, C., Mangiarotti, A., Vanhille-Campos, C., Aylan, B., Pellegrino, E., Athanasiadi, N., Fearns, A., Rodgers, A., Franzmann, T.M., Šarić, A., et al. (2023). Stress granules plug and stabilize damaged endolysosomal membranes. Nature *623*, 1062–1069.
34. Jia, J., Wang, F., Bhujabal, Z., Peters, R., Mudd, M., Duque, T., Allers, L., Javed, R., Salemi, M., Behrends, C., et al. (2022). Stress granules and mTOR are regulated by membrane atg8ylation during lysosomal damage. J. Cell Biol. *221*, e202207091.
35. Hofmann, S., Kedersha, N., Anderson, P., and Ivanov, P. (2021). Molecular mechanisms of stress granule assembly and disassembly. Biochim. Biophys. Acta Mol. Cell Res. *1868*.
36. Proud, C.G. (2005). eIF2 and the control of cell physiology. Semin. Cell Dev. Biol. *16*, 3–12.
37. Mazroui, R., Sukarieh, R., Bordeleau, M.E., Kaufman, R.J., Northcote, P., Tanaka, J., Gallouzi, I., and Pelletier, J. (2006). Inhibition of ribosome recruitment induces stress granule formation independently of eukaryotic initiation factor 2alpha phosphorylation. Mol. Biol. Cell *17*, 4212–4219.
38. McInerney, G.M., Kedersha, N.L., Kaufman, R.J., Anderson, P., and Liljeström, P. (2005). Importance of eIF2α phosphorylation and stress granule assembly in alphavirus translation regulation. Mol. Biol. Cell *16*, 3753–3763.
39. Guan, B.-J., Krokowski, D., Majumder, M., Schmotzer, C.L., Kimball, S.R., Merrick, W.C., Koromilas, A.E., and Hatzoglou, M. (2014). Translational control during endoplasmic reticulum stress beyond phosphorylation of the translation initiation factor eIF2α. J. Biol. Chem. *289*, 12593–12611.
40. Koumenis, C., Naczki, C., Koritzinsky, M., Rastani, S., Diehl, A., Sonenberg, N., Koromilas, A., and Wouters, B.G. (2002). Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase PERK and phosphorylation of the translation initiation factor eIF2alpha. Mol. Cell Biol. *22*, 7405–7416.
41. Fournier, M.J., Coudert, L., Mellaoui, S., Adjibade, P., Gareau, C., Côté, M.F., Sonenberg, N., Gaudreault, R.C., and Mazroui, R. (2013). Inactivation of the mTORC1-eukaryotic translation initiation factor 4E pathway alters stress granule formation. Mol. Cell Biol. *33*, 2285–2301.
42. Fujimura, K., Sasaki, A.T., 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.
43. Emara, M.M., Fujimura, K., Sciaranghella, D., Ivanova, V., Ivanov, P., and Anderson, P. (2012). Hydrogen peroxide induces stress granule formation independent of eIF2α phosphorylation. Biochem. Biophys. Res. Commun. *423*, 763–769.
44. Molliex, A., Temirov, J., Lee, J., Coughlin, M., Kanagaraj, A.P., Kim, H.J., Mittag, T., and Taylor, J.P. (2015). Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization. Cell *163*, 123–133.
45. Zhang, M.L., Zhang, Z., Niu, X.Z., Ti, H.Y., Zhou, Y.X., Gao, B., Li, Y., Liu, J.L., Chen, X., and Li, H. (2024). Interplay Between Intracellular Transport Dynamics and Liquid-Liquid Phase Separation. Adv. Sci. *11*, e2308338.
46. Jayabalan, A.K., Sanchez, A., Park, R.Y., Yoon, S.P., Kang, G.Y., Baek, J.H., Anderson, P., Kee, Y., and Ohn, T. (2016). NEDDylation promotes stress granule assembly. Nat. Commun. *7*, 12125.
47. Luo, Y.-Y., Wu, J.-J., and Li, Y.-M. (2021). Regulation of liquid-liquid phase separation with focus on post-translational modifications. Chem. Commun. *57*, 13275–13287.
48. Dimasi, P., Quintiero, A., Shelkovnikova, T.A., and Buchman, V.L. (2017). Modulation of p-eIF2α cellular levels and stress granule assembly/disassembly by trehalose. Sci. Rep. *7*, 44088.
49. Wippich, F., Bodenmiller, B., Trajkovska, M.G., Wanka, S., Aebersold, R., and Pelkmans, L. (2013). Dual specificity kinase DYRK3 couples stress granule condensation/dissolution to mTORC1 signaling. Cell *152*, 791–805.
50. Mediani, L., Antoniani, F., Galli, V., Vinet, J., Carrà, A.D., Bigi, I., Tripathy, V., Tiago, T., Cimino, M., Leo, G., et al. (2021). Hsp90-mediated regulation of DYRK3 couples stress granule disassembly and growth via mTORC1 signaling. EMBO Rep. *22*, e51740.
51. Wang, B., Maxwell, B.A., Joo, J.H., Gwon, Y., Messing, J., Mishra, A., Shaw, T.I., Ward, A.L., Quan, H., Sakurada, S.M., et al. (2019). ULK1 and ULK2 Regulate Stress Granule Disassembly Through Phosphorylation and Activation of VCP/p97. Mol. Cell *74*, 742–757.e8.
52. Das, R., Schwintzer, L., Vinopal, S., Aguado Roca, E., Sylvester, M., Oprisoreanu, A.M., Schoch, S., Bradke, F., and Broemer, M. (2019). New roles for the de-ubiquitylating enzyme OTUD4 in an RNA-protein network and RNA granules. J. Cell Sci. *132*, jcs229252.
53. Chitiprolu, M., Jagow, C., Tremblay, V., Bondy-Chorney, E., Paris, G., Savard, A., Palidwor, G., Barry, F.A., Zinman, L., Keith, J., et al. (2018). A complex of C9ORF72 and p62 uses arginine methylation to eliminate stress granules by autophagy. Nat. Commun. *9*, 2794.
54. Huang, C., Chen, Y., Dai, H., Zhang, H., Xie, M., Zhang, H., Chen, F., Kang, X., Bai, X., and Chen, Z. (2020). UBAP2L arginine methylation by PRMT1 modulates stress granule assembly. Cell Death Differ. *27*, 227–241.
55. Tsai, W.-C., Gayatri, S., Reineke, L.C., Sbardella, G., Bedford, M.T., and Lloyd, R.E. (2016). Arginine Demethylation of G3BP1 Promotes Stress Granule Assembly. J. Biol. Chem. *291*, 22671–22685.
56. Huang, L., Wang, Z., Narayanan, N., and Yang, Y. (2018). Arginine methylation of the C-terminus RGG motif promotes TOP3B topoisomerase activity and stress granule localization. Nucleic Acids Res. *46*, 3061–3074.
57. Yamaguchi, A., and Kitajo, K. (2012). The effect of PRMT1-mediated arginine methylation on the subcellular localization, stress granules, and detergent-insoluble aggregates of FUS/TLS. PLoS One *7*, e49267.
58. Ganassi, M., Mateju, D., Bigi, I., Mediani, L., Poser, I., Lee, H.O., Seguin, S.J., Morelli, F.F., Vinet, J., Leo, G., et al. (2016). A Surveillance Function of the HSPB8-BAG3-HSP70 Chaperone Complex Ensures Stress Granule Integrity and Dynamism. Mol. Cell *63*, 796–810.
59. Keiten-Schmitz, J., Wagner, K., Piller, T., Kaulich, M., Alberti, S., and Müller, S. (2020). The nuclear SUMO-targeted ubiquitin quality control network regulates the dynamics of cytoplasmic stress granules. Mol. Cell *79*, 54–67.
60. Schulte, T., Panas, M.D., Han, X., Williams, L., Kedersha, N., Fleck, J.S., Tan, T.J.C., Dopico, X.C., Olsson, A., Morro, A.M., et al. (2023). Caprin-1 binding to the critical stress granule protein G3BP1 is influenced by pH. Open Biol. *13*, 220369.
61. Hu, R., Qian, B., Li, A., and Fang, Y. (2022). Role of Proteostasis Regulation in the Turnover of Stress Granules. Int. J. Mol. Sci. *23*, 14565.
62. Zhang, J., Chen, X., Chen, G., Wang, H., Jia, L., Hao, Y., and Yao, D. (2023). Identification of a novel PAK1/HDAC6 dual inhibitor ZMF-23 that triggers tubulin-stathmin regulated cell death in triple negative breast cancer. Int. J. Biol. Macromol. *251*, 126348.
63. Zhang, C.-H., Liu, H., Zhao, W.L., Zhao, W.X., Zhou, H.M., and Shao, R.G. (2021). G3BP1 promotes human breast cancer cell proliferation through coordinating with GSK-3β and stabilizing β-catenin. Acta Pharmacol. Sin. *42*, 1900–1912.
64. Zhan, Y., Wang, W., Wang, H., Xu, Y., Zhang, Y., Ning, Y., Zheng, H., Luo, J., Yang, Y., Zang, H., et al. (2024). G3BP1 Interact with JAK2 mRNA to Promote the Malignant Progression of Nasopharyngeal Carcinoma

via Activating JAK2/STAT3 Signaling Pathway. Int. J. Biol. Sci. *20*, 94–112.
65. Qiu, Y.-Q., Yang, C.W., Lee, Y.Z., Yang, R.B., Lee, C.H., Hsu, H.Y., Chang, C.C., and Lee, S.J. (2015). Targeting a ribonucleoprotein complex containing the caprin-1 protein and the c-Myc mRNA suppresses tumor growth in mice: an identification of a novel oncotarget. Oncotarget *6*, 2148–2163.
66. Zeng, Q., Saghafinia, S., Chryplewicz, A., Fournier, N., Christe, L., Xie, Y.Q., Guillot, J., Yucel, S., Li, P., Galván, J.A., et al. (2022). Aberrant hyperexpression of the RNA binding protein FMRP in tumors mediates immune evasion. Science *378*, eabl7207.
67. Guillén-Boixet, J., Kopach, A., Holehouse, A.S., Wittmann, S., Jahnel, M., Schlüßler, R., Kim, K., Trussina, I.R.E.A., Wang, J., Mateju, D., et al. (2020). RNA-Induced Conformational Switching and Clustering of G3BP Drive Stress Granule Assembly by Condensation. Cell *181*, 346–361.e17.
68. Wang, Z., Zhang, C., Fan, C., and Liu, Y. (2023). Post-translational modifications in stress granule and their implications in neurodegenerative diseases. Biochim. Biophys. Acta. Gene Regul. Mech. *1866*, 194989.
69. Tourrière, H., Chebli, K., Zekri, L., Courselaud, B., Blanchard, J.M., Bertrand, E., and Tazi, J. (2023). The RasGAP-associated endoribonuclease G3BP mediates stress granule assembly. J. Cell Biol. *222*, e200212128072023new.
70. Meyer, C., Garzia, A., Morozov, P., Molina, H., and Tuschl, T. (2020). The G3BP1-Family-USP10 Deubiquitinase Complex Rescues Ubiquitinated 40S Subunits of Ribosomes Stalled in Translation from Lysosomal Degradation. Mol. Cell *77*, 1193–1205.e5.
71. Mi, K., Zeng, L., Chen, Y., Ning, J., Zhang, S., Zhao, P., and Yang, S. (2024). DHX38 enhances proliferation, metastasis, and EMT progression in NSCLC through the G3BP1-mediated MAPK pathway. Cell. Signal. *113*, 110962.
72. Zhang, L.-N., Zhao, L., Yan, X.-L., and Huang, Y.-H. (2019). Loss of G3BP1 suppresses proliferation, migration, and invasion of esophageal cancer cells via Wnt/β-catenin and PI3K/AKT signaling pathways. J. Cell. Physiol. *234*, 20469–20484.
73. Mao, C., Wang, X., Liu, Y., Wang, M., Yan, B., Jiang, Y., Shi, Y., Shen, Y., Liu, X., Lai, W., et al. (2018). A G3BP1-Interacting lncRNA Promotes Ferroptosis and Apoptosis in Cancer via Nuclear Sequestration of p53. Cancer Res. *78*, 3484–3496.
74. Mukhopadhyay, C., Yang, C., Xu, L., Liu, D., Wang, Y., Huang, D., Deonarine, L.D., Cyrta, J., Davicioni, E., Sboner, A., et al. (2021). G3BP1 inhibits Cul3SPOP to amplify AR signaling and promote prostate cancer. Nat. Commun. *12*, 6662.
75. Ashikari, D., Takayama, K., Tanaka, T., Suzuki, Y., Obinata, D., Fujimura, T., Urano, T., Takahashi, S., and Inoue, S. (2017). Androgen induces G3BP2 and SUMO-mediated p53 nuclear export in prostate cancer. Oncogene *36*, 6272–6281.
76. Omer, A., Barrera, M.C., Moran, J.L., Lian, X.J., Di Marco, S., Beausejour, C., and Gallouzi, I.E. (2020). G3BP1 controls the senescence-associated secretome and its impact on cancer progression. Nat. Commun. *11*, 4979.
77. Li, C., Pan, B., Wang, X., Liu, X., Qin, J., Gao, T., Sun, H., Pan, Y., and Wang, S. (2022). Upregulated LINC01088 facilitates malignant phenotypes and immune escape of colorectal cancer by regulating microRNAs/G3BP1/PD-L1 axis. J. Cancer Res. Clin. Oncol. *148*, 1965–1982.
78. Zhao, J., Fu, X., Chen, H., Min, L., Sun, J., Yin, J., Guo, J., Li, H., Tang, Z., Ruan, Y., et al. (2021). G3BP1 interacts with YWHAZ to regulate chemoresistance and predict adjuvant chemotherapy benefit in gastric cancer. Br. J. Cancer *124*, 425–436.
79. Somasekharan, S.P., Zhang, F., Saxena, N., Huang, J.N., Kuo, I.C., Low, C., Bell, R., Adomat, H., Stoynov, N., Foster, L., et al. (2020). G3BP1-linked mRNA partitioning supports selective protein synthesis in response to oxidative stress. Nucleic Acids Res. *48*, 6855–6873.
80. Oi, N., Yuan, J., Malakhova, M., Luo, K., Li, Y., Ryu, J., Zhang, L., Bode, A.M., Xu, Z., Li, Y., et al. (2015). Resveratrol induces apoptosis by directly targeting Ras-GTPase-activating protein SH3 domain-binding protein 1. Oncogene *34*, 2660–2671.
81. Malvi, P., Reddy, D.S., Kumar, R., Chava, S., Burela, S., Parajuli, K., Zhang, X., and Wajapeyee, N. (2023). LIMK2 promotes melanoma tumor growth and metastasis through G3BP1-ESM1 pathway-mediated apoptosis inhibition. Oncogene *42*, 1478–1491.
82. Gupta, N., Badeaux, M., Liu, Y., Naxerova, K., Sgroi, D., Munn, L.L., Jain, R.K., and Garkavtsev, I. (2017). Stress granule-associated protein G3BP2 regulates breast tumor initiation. Proc. Natl. Acad. Sci. USA *114*, 1033–1038.
83. Kedersha, N.L., 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.
84. Gilks, N., Kedersha, N., Ayodele, M., Shen, L., Stoecklin, G., Dember, L.M., and Anderson, P. (2004). Stress granule assembly is mediated by prion-like aggregation of TIA-1. Mol. Biol. Cell *15*, 5383–5398.
85. Eisinger-Mathason, T.S.K., Andrade, J., Groehler, A.L., Clark, D.E., Muratore-Schroeder, T.L., Pasic, L., Smith, J.A., Shabanowitz, J., Hunt, D.F., Macara, I.G., and Lannigan, D.A. (2008). Codependent functions of RSK2 and the apoptosis-promoting factor TIA-1 in stress granule assembly and cell survival. Mol. Cell *31*, 722–736.
86. Sánchez-Jiménez, C., and Izquierdo, J.M. (2013). T-cell intracellular antigen (TIA)-proteins deficiency in murine embryonic fibroblasts alters cell cycle progression and induces autophagy. PLoS One *8*, e75127.
87. Yang, W., Chen, H., Li, G., Zhang, T., Sui, Y., Liu, L., Hu, J., Wang, G., Chen, H., Wang, Y., et al. (2023). Caprin-1 influences autophagy-induced tumor growth and immune modulation in pancreatic cancer. J. Transl. Med. *21*, 903.
88. Gao, Y., Yuan, L., Ke, C., Pei, Z., Liu, X., Wu, R., Kui, X., and Zhang, Y. (2023). Caprin-1 plays a role in cell proliferation and Warburg metabolism of esophageal carcinoma by regulating METTL3 and WTAP. J. Transl. Med. *21*, 159.
89. Sabile, A.A., Arlt, M.J.E., Muff, R., Husmann, K., Hess, D., Bertz, J., Langsam, B., Aemisegger, C., Ziegler, U., Born, W., and Fuchs, B. (2013). Caprin-1, a novel Cyr61-interacting protein, promotes osteosarcoma tumor growth and lung metastasis in mice. Biochim. Biophys. Acta *1832*, 1173–1182.
90. Guo, J., Qu, H., Chen, Y., and Xia, J. (2017). The role of RNA-binding protein tristetraprolin in cancer and immunity. Med. Oncol. *34*, 1–12.
91. Guo, J., Wang, H., Jiang, S., Xia, J., and Jin, S. (2017). The cross-talk between tristetraprolin and cytokines in cancer. Anti Cancer Agents Med. Chem. *17*, 1477–1486.
92. Shukla, S., Elson, G., Blackshear, P.J., Lutz, C.S., and Leibovich, S.J. (2017). 3'UTR AU-Rich Elements (AREs) and the RNA-Binding Protein Tristetraprolin (TTP) Are Not Required for the LPS-Mediated Destabilization of Phospholipase-Cβ-2 mRNA in Murine Macrophages. Inflammation *40*, 645–656.
93. Stoecklin, G., Stubbs, T., Kedersha, N., Wax, S., Rigby, W.F.C., Blackwell, T.K., and Anderson, P. (2004). MK2-induced tristetraprolin:14-3-3 complexes prevent stress granule association and ARE-mRNA decay. EMBO J. *23*, 1313–1324.
94. Marderosian, M., Sharma, A., Funk, A.P., Vartanian, R., Masri, J., Jo, O.D., and Gera, J.F. (2006). Tristetraprolin regulates Cyclin D1 and c-Myc mRNA stability in response to rapamycin in an Akt-dependent manner via p38 MAPK signaling. Oncogene *25*, 6277–6290.
95. Lai, A., Valdez-Sinon, A.N., and Bassell, G.J. (2020). Regulation of RNA granules by FMRP and implications for neurological diseases. Traffic *21*, 454–462.
96. Alpatov, R., Lesch, B.J., Nakamoto-Kinoshita, M., Blanco, A., Chen, S., Stützer, A., Armache, K.J., Simon, M.D., Xu, C., Ali, M., and Murn, J. (2014). A chromatin-dependent role of the fragile X mental retardation protein FMRP in the DNA damage response. Cell *157*, 869–881.
97. Kim, M., Bellini, M., and Ceman, S. (2009). Fragile X mental retardation protein FMRP binds mRNAs in the nucleus. Mol. Cell Biol. *29*, 214–228.
98. Lucá, R., Averna, M., Zalfa, F., Vecchi, M., Bianchi, F., La Fata, G., Del Nonno, F., Nardacci, R., Bianchi, M., Nuciforo, P., et al. (2013). The Fragile X Protein binds m RNA s involved in cancer progression and modulates metastasis formation. EMBO Mol. Med. *5*, 1523–1536.
99. Fu, Y., and Zhuang, X. (2020). m6A-binding YTHDF proteins promote stress granule formation. Nat. Chem. Biol. *16*, 955–963.
100. Chen, Y., Wan, R., Zou, Z., Lao, L., Shao, G., Zheng, Y., Tang, L., Yuan, Y., Ge, Y., He, C., and Lin, S. (2023). O-GlcNAcylation determines the translational regulation and phase separation of YTHDF proteins. Nat. Cell Biol. *25*, 1676–1690.
101. Wang, W., Shao, F., Yang, X., Wang, J., Zhu, R., Yang, Y., Zhao, G., Guo, D., Sun, Y., Wang, J., et al. (2021). METTL3 promotes tumour development by decreasing APC expression mediated by APC mRNA N6-methyladenosine-dependent YTHDF binding. Nat. Commun. *12*, 3803.
102. Chen, M., Wei, L., Law, C.T., Tsang, F.H.C., Shen, J., Cheng, C.L.H., Tsang, L.H., Ho, D.W.H., Chiu, D.K.C., Lee, J.M.F., et al. (2018). RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2. Hepatol. Baltim. Md *67*, 2254–2270.

103. Somasekharan, S.P., El-Naggar, A., Leprivier, G., Cheng, H., Hajee, S., Grunewald, T.G.P., Zhang, F., Ng, T., Delattre, O., Evdokimova, V., et al. (2015). YB-1 regulates stress granule formation and tumor progression by translationally activating G3BP1. J. Cell Biol. *208*, 913–929.
104. Lyons, S.M., Achorn, C., Kedersha, N.L., Anderson, P.J., and Ivanov, P. (2016). YB-1 regulates tiRNA-induced Stress Granule formation but not translational repression. Nucleic Acids Res. *44*, 6949–6960.
105. Tanaka, T., Ohashi, S., and Kobayashi, S. (2014). Roles of YB-1 under arsenite-induced stress: translational activation of HSP70 mRNA and control of the number of stress granules. Biochim. Biophys. Acta *1840*, 985–992.
106. Kitajima, H., Maruyama, R., Niinuma, T., Yamamoto, E., Takasawa, A., Takasawa, K., Ishiguro, K., Tsuyada, A., Suzuki, R., Sudo, G., et al. (2023). TM4SF1-AS1 inhibits apoptosis by promoting stress granule formation in cancer cells. Cell Death Dis. *14*, 424.
107. Lim, J.P., Shyamasundar, S., Gunaratne, J., Scully, O.J., Matsumoto, K., and Bay, B.H. (2017). YBX1 gene silencing inhibits migratory and invasive potential via CORO1C in breast cancer in vitro. BMC Cancer *17*, 201.
108. Lim, J.P., Nair, S., Shyamasundar, S., Chua, P.J., Muniasamy, U., Matsumoto, K., Gunaratne, J., and Bay, B.H. (2019). Silencing Y-box binding protein-1 inhibits triple-negative breast cancer cell invasiveness via regulation of MMP1 and beta-catenin expression. Cancer Lett. *452*, 119–131.
109. Wang, J.-Z., Zhu, H., You, P., Liu, H., Wang, W.K., Fan, X., Yang, Y., Xu, K., Zhu, Y., Li, Q., et al. (2022). Upregulated YB-1 protein promotes glioblastoma growth through a YB-1/CCT4/mLST8/mTOR pathway. J. Clin. Invest. *132*, e146536.
110. Liao, L.-Z., Chen, C.T., Li, N.C., Lin, L.C., Huang, B.S., Chang, Y.H., and Chow, L.P. (2020). Y-Box Binding Protein-1 Promotes Epithelial-Mesenchymal Transition in Sorafenib-Resistant Hepatocellular Carcinoma Cells. Int. J. Mol. Sci. *22*, 224.
111. Setoguchi, K., Cui, L., Hachisuka, N., Obchoei, S., Shinkai, K., Hyodo, F., Kato, K., Wada, F., Yamamoto, T., Harada-Shiba, M., et al. (2017). Antisense Oligonucleotides Targeting Y-Box Binding Protein-1 Inhibit Tumor Angiogenesis by Downregulating Bcl-xL-VEGFR2/-Tie Axes. Mol. Ther. Nucleic Acids *9*, 170–181.
112. Takahashi, M., Higuchi, M., Matsuki, H., Yoshita, M., Ohsawa, T., Oie, M., and Fujii, M. (2013). Stress granules inhibit apoptosis by reducing reactive oxygen species production. Mol. Cell Biol. *33*, 815–829.
113. Piatnitskaia, S., Takahashi, M., Kitaura, H., Katsuragi, Y., Kakihana, T., Zhang, L., Kakita, A., Iwakura, Y., Nawa, H., Miura, T., et al. (2019). USP10 is a critical factor for Tau-positive stress granule formation in neuronal cells. Sci. Rep. *9*, 10591.
114. Takayama, K.-I., Suzuki, T., Fujimura, T., Takahashi, S., and Inoue, S. (2018). Association of USP10 with G3BP2 Inhibits p53 Signaling and Contributes to Poor Outcome in Prostate Cancer. Mol. Cancer Res. *16*, 846–856.
115. Yang, R., Chen, H., Xing, L., Wang, B., Hu, M., Ou, X., Chen, H., Deng, Y., Liu, D., Jiang, R., and Chen, J. (2022). Hypoxia-induced circWSB1 promotes breast cancer progression through destabilizing p53 by interacting with USP10. Mol. Cancer *21*, 88.
116. Bhattacharya, U., Thavathiru, E., Neizer-Ashun, F., Xu, C., Gatalica, Z., Dwivedi, S.K.D., Dey, A., Mukherjee, P., and Bhattacharya, R. (2022). The deubiquitinase USP10 protects pancreatic cancer cells from endoplasmic reticulum stress. npj Precis. Oncol. *6*, 93.
117. Mahboubi, H., Koromilas, A.E., and Stochaj, U. (2016). AMP Kinase Activation Alters Oxidant-Induced Stress Granule Assembly by Modulating Cell Signaling and Microtubule Organization. Mol. Pharmacol. *90*, 460–468.
118. Reiter, A.K., Bolster, D.R., Crozier, S.J., Kimball, S.R., and Jefferson, L.S. (2005). Repression of protein synthesis and mTOR signaling in rat liver mediated by the AMPK activator aminoimidazole carboxamide ribonucleoside. Am. J. Physiol. Endocrinol. Metab. *288*, E980–E988.
119. Luo, Z., Saha, A.K., Xiang, X., and Ruderman, N.B. (2005). AMPK, the metabolic syndrome and cancer. Trends Pharmacol. Sci. *26*, 69–76.
120. Ríos, M., Foretz, M., Viollet, B., Prieto, A., Fraga, M., Costoya, J.A., and Señarís, R. (2013). AMPK activation by oncogenesis is required to maintain cancer cell proliferation in astrocytic tumors. Cancer Res. *73*, 2628–2638.
121. Xia, Y.C., Zha, J.H., Sang, Y.H., Yin, H., Xu, G.Q., Zhen, J., Zhang, Y., and Yu, B.T. (2021). AMPK activation by ASP4132 inhibits non-small cell lung cancer cell growth. Cell Death Dis. *12*, 365.
122. Dong, Y., Hu, H., Zhang, X., Zhang, Y., Sun, X., Wang, H., Kan, W., Tan, M.J., Shi, H., Zang, Y., and Li, J. (2023). Phosphorylation of PHF2 by AMPK releases the repressive H3K9me2 and inhibits cancer metastasis. Signal Transduct. Targeted Ther. *8*, 95.
123. Hampsch, R.A., Wells, J.D., Traphagen, N.A., McCleery, C.F., Fields, J.L., Shee, K., Dillon, L.M., Pooler, D.B., Lewis, L.D., Demidenko, E., et al. (2020). AMPK activation by metformin promotes survival of dormant ER+ breast cancer cells. Clin. Cancer Res. *26*, 3707–3719.
124. 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.
125. Feng, S., Daw, J.N., and Chen, Q.M. (2020). Histone deacetylase inhibitors prevent H2O2 from inducing stress granule formation. Curr. Res. Toxicol. *1*, 141–148.
126. Kaur, S., Rajoria, P., and Chopra, M. (2022). HDAC6: A unique HDAC family member as a cancer target. Cell. Oncol. *45*, 779–829.
127. Tsai, Y.-C., Wang, T.Y., Hsu, C.L., Lin, W.C., Chen, J.Y., Li, J.H., Pu, Y.S., Cheng, A.L., Cheng, J.C.H., and Su, S.F. (2023). Selective inhibition of HDAC6 promotes bladder cancer radiosensitization and mitigates the radiation-induced CXCL1 signalling. Br. J. Cancer *128*, 1753–1764.
128. Altucci, L. (2017). A key HDAC6 dependency of ARID1A-mutated ovarian cancer. Nat. Cell Biol. *19*, 889–890.
129. Taniuchi, K., Furihata, M., and Saibara, T. (2014). KIF20A-mediated RNA granule transport system promotes the invasiveness of pancreatic cancer cells. Neoplasia *16*, 1082–1093.
130. Boese, A.C., Kang, J., Hwang, J.S., Kim, J., Eun, K., Malin, C.M., Magliocca, K.R., Pan, C., Jin, L., and Kang, S. (2023). Succinyl-CoA ligase ADP-forming subunit beta promotes stress granule assembly to regulate redox and drive cancer metastasis. Proc. Natl. Acad. Sci. USA *120*, e2217332120.
131. Kohno, S., Linn, P., Nagatani, N., Watanabe, Y., Kumar, S., Soga, T., and Takahashi, C. (2020). Pharmacologically targetable vulnerability in prostate cancer carrying RB1-SUCLA2 deletion. Oncogene *39*, 5690–5707.
132. Challa, S., Nandu, T., Kim, H.B., Gong, A., Renshaw, C.W., Li, W.C., Tan, X., Camacho, C.V., Chen, J., and Kraus, W.L. (2023). A PARP14/TARG1-Regulated RACK1 MARylation Cycle Drives Stress Granule Dynamics in Ovarian Cancer Cells. Preprint at bioRxiv *39*, 5690. https://doi.org/10.1101/2023.10.13.562273.
133. Buoso, E., Masi, M., Long, A., Chiappini, C., Travelli, C., Govoni, S., and Racchi, M. (2022). Ribosomes as a nexus between translation and cancer progression: Focus on ribosomal Receptor for Activated C Kinase 1 (RACK1) in breast cancer. Br. J. Pharmacol. *179*, 2813–2828.
134. Tian, R., Tian, J., Zuo, X., Ren, S., Zhang, H., Liu, H., Wang, Z., Cui, Y., Niu, R., and Zhang, F. (2023). RACK1 facilitates breast cancer progression by competitively inhibiting the binding of β-catenin to PSMD2 and enhancing the stability of β-catenin. Cell Death Dis. *14*, 685.
135. Dan, H., Liu, S., Liu, J., Liu, D., Yin, F., Wei, Z., Wang, J., Zhou, Y., Jiang, L., Ji, N., et al. (2020). RACK1 promotes cancer progression by increasing the M2/M1 macrophage ratio via the NF-κB pathway in oral squamous cell carcinoma. Mol. Oncol. *14*, 795–807.
136. Wu, H., Song, S., Yan, A., Guo, X., Chang, L., Xu, L., Hu, L., Kuang, M., Liu, B., He, D., et al. (2020). RACK1 promotes the invasive activities and lymph node metastasis of cervical cancer via galectin-1. Cancer Lett. *469*, 287–300.
137. Chen, M., Wang, G., Xu, Z., Sun, J., Liu, B., Chang, L., Gu, J., Ruan, Y., Gao, X., and Song, S. (2024). Loss of RACK1 promotes glutamine addiction via activating AKT/mTOR/ASCT2 axis to facilitate tumor growth in gastric cancer. Cell. Oncol. *47*, 113–128.
138. Xu, L., Li, J., Tursun, M., Hai, Y., Tursun, H., Mamtimin, B., and Hasim, A. (2022). Receptor for activated C kinase 1 promotes cervical cancer lymph node metastasis via the glycolysis-dependent AKT/mTOR signaling. Int. J. Oncol. *61*, 83–87.
139. Choi, S., Sa, M., Cho, N., Kim, K.K., and Park, S.-H. (2019). Rbfox2 dissociation from stress granules suppresses cancer progression. Exp. Mol. Med. *51*, 1–12.
140. Böhm, R., Imseng, S., Jakob, R.P., Hall, M.N., Maier, T., and Hiller, S. (2021). The dynamic mechanism of 4E-BP1 recognition and phosphorylation by mTORC1. Mol. Cell *81*, 2403–2416.e5.
141. Batool, A., Majeed, S.T., Aashaq, S., Majeed, R., Shah, G., Nazir, N., and Andrabi, K.I. (2019). Eukaryotic Initiation Factor 4E (eIF4E) sequestration mediates 4E-BP1 response to rapamycin. Int. J. Biol. Macromol. *125*, 651–659.
142. Haghandish, N., Baldwin, R.M., Morettin, A., Dawit, H.T., Adhikary, H., Masson, J.Y., Mazroui, R., Trinkle-Mulcahy, L., and Côté, J. (2019). PRMT7 methylates eukaryotic translation initiation factor 2α and regulates

its role in stress granule formation. Mol. Biol. Cell *30*, 778–793.
143. Chen, H.-Y., Lin, L.T., Wang, M.L., Tsai, K.L., Huang, P.I., Yang, Y.P., Lee, Y.Y., Chen, Y.W., Lo, W.L., Lan, Y.T., et al. (2018). Musashi-1 promotes chemoresistant granule formation by PKR/eIF2α signalling cascade in refractory glioblastoma. Biochim. Biophys. Acta, Mol. Basis Dis. *1864*, 1850–1861.
144. Kepp, O., Galluzzi, L., Giordanetto, F., Tesniere, A., Vitale, I., Martins, I., Schlemmer, F., Adjemian, S., Zitvogel, L., and Kroemer, G. (2009). Disruption of the PP1/GADD34 complex induces calreticulin exposure. Cell Cycle *8*, 3971–3977.
145. Tian, L., Xie, X., Das, U., Chen, Y., Sun, Y., Liu, F., Lu, H., Nan, P., Zhu, Y., Gu, X., et al. (2022). Forming cytoplasmic stress granules PURα suppresses mRNA translation initiation of IGFBP3 to promote esophageal squamous cell carcinoma progression. Oncogene *41*, 4336–4348.
146. Seoane, R., Lama-Díaz, T., Romero, A.M., El Motiam, A., Martínez-Férriz, A., Vidal, S., Bouzaher, Y.H., Blanquer, M., Tolosa, R.M., Castillo Mewa, J., et al. (2024). SUMOylation modulates eIF5A activities in both yeast and pancreatic ductal adenocarcinoma cells. Cell. Mol. Biol. Lett. *29*, 15.
147. Laver, J.D., Ly, J., Winn, A.K., Karaiskakis, A., Lin, S., Nie, K., Benic, G., Jaberi-Lashkari, N., Cao, W.X., Khademi, A., et al. (2020). The RNA-binding protein Rasputin/G3BP enhances the stability and translation of its target mRNAs. Cell Rep. *30*, 3353–3367.e7.
148. Velasco, B.R., and Izquierdo, J.M. (2022). T-cell intracellular antigen 1-like protein in physiology and pathology. Int. J. Mol. Sci. *23*, 7836.
149. Hao, P., Yu, J., Ward, R., Liu, Y., Hao, Q., An, S., and Xu, T. (2020). Eukaryotic translation initiation factors as promising targets in cancer therapy. Cell Commun. Signal. *18*, 1–20.
150. Fabbri, L., Chakraborty, A., Robert, C., and Vagner, S. (2021). The plasticity of mRNA translation during cancer progression and therapy resistance. Nat. Rev. Cancer *21*, 558–577.
151. Glaviano, A., Foo, A.S.C., Lam, H.Y., Yap, K.C.H., Jacot, W., Jones, R.H., Eng, H., Nair, M.G., Makvandi, P., Geoerger, B., et al. (2023). PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol. Cancer *22*, 138.
152. Lee, B.J., Boyer, J.A., Burnett, G.L., Thottumkara, A.P., Tibrewal, N., Wilson, S.L., Hsieh, T., Marquez, A., Lorenzana, E.G., Evans, J.W., et al. (2021). Selective inhibitors of mTORC1 activate 4EBP1 and suppress tumor growth. Nat. Chem. Biol. *17*, 1065–1074.
153. Sfakianos, A.P., Mellor, L.E., Pang, Y.F., Kritsiligkou, P., Needs, H., Abou-Hamdan, H., Désaubry, L., Poulin, G.B., Ashe, M.P., and Whitmarsh, A.J. (2018). The mTOR-S6 kinase pathway promotes stress granule assembly. Cell Death Differ. *25*, 1766–1780.
154. Liu, B., Zhang, J., Meng, X., Xie, S.M., Liu, F., Chen, H., Yao, D., Li, M., Guo, M., Shen, H., et al. (2023). HDAC6-G3BP2 promotes lysosomal-TSC2 and suppresses mTORC1 under ETV4 targeting-induced low-lactate stress in non-small cell lung cancer. Oncogene *42*, 1181–1195.
155. Liu, H.-J., Du, H., Khabibullin, D., Zarei, M., Wei, K., Freeman, G.J., Kwiatkowski, D.J., and Henske, E.P. (2023). mTORC1 upregulates B7-H3/CD276 to inhibit antitumor T cells and drive tumor immune evasion. Nat. Commun. *14*, 1214.
156. Sharma, M., and Pruitt, K. (2020). Wnt pathway: an integral hub for developmental and oncogenic signaling networks. Int. J. Mol. Sci. *21*, 8018.
157. Sahoo, P.K., Murawala, P., Sawale, P.T., Sahoo, M.R., Tripathi, M.M., Gaikwad, S.R., Seshadri, V., and Joseph, J. (2012). Wnt signalling antagonizes stress granule assembly through a Dishevelled-dependent mechanism. Biol. Open *1*, 109–119.
158. 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.
159. Díaz-Muñoz, M.D., Kiselev, V.Y., Le Novère, N., Curk, T., Ule, J., and Turner, M. (2017). Tia1 dependent regulation of mRNA subcellular location and translation controls p53 expression in B cells. Nat. Commun. *8*, 530.
160. Cook, J.H., Melloni, G.E.M., Gulhan, D.C., Park, P.J., and Haigis, K.M. (2021). The origins and genetic interactions of KRAS mutations are allele-and tissue-specific. Nat. Commun. *12*, 1808.
161. Hallin, J., Bowcut, V., Calinisan, A., Briere, D.M., Hargis, L., Engstrom, L.D., Laguer, J., Medwid, J., Vanderpool, D., Lifset, E., et al. (2022). Anti-tumor efficacy of a potent and selective non-covalent KRASG12D inhibitor. Nat. Med. *28*, 2171–2182.
162. Glasser, E., Maji, D., Biancon, G., Puthenpeedikakkal, A.M.K., Cavender, C.E., Tebaldi, T., Jenkins, J.L., Mathews, D.H., Halene, S., and Kielkopf, C.L. (2022). Pre-mRNA splicing factor U2AF2 recognizes distinct conformations of nucleotide variants at the center of the pre-mRNA splice site signal. Nucleic Acids Res. *50*, 5299–5312.
163. Okeyo-Owuor, T., White, B.S., Chatrikhi, R., Mohan, D.R., Kim, S., Griffith, M., Ding, L., Ketkar-Kulkarni, S., Hundal, J., Laird, K.M., et al. (2015). U2AF1 mutations alter sequence specificity of pre-mRNA binding and splicing. Leukemia *29*, 909–917.
164. Biancon, G., Joshi, P., Zimmer, J.T., Hunck, T., Gao, Y., Lessard, M.D., Courchaine, E., Barentine, A.E.S., Machyna, M., Botti, V., et al. (2022). Precision analysis of mutant U2AF1 activity reveals deployment of stress granules in myeloid malignancies. Mol. Cell *82*, 1107–1122.e7.
165. Jin, P., Wang, X., Jin, Q., Zhang, Y., Shen, J., Jiang, G., Zhu, H., Zhao, M., Wang, D., Li, Z., et al. (2024). Mutant U2AF1-induced mis-splicing of mRNA translation genes confers resistance to chemotherapy in acute myeloid leukemia. Cancer Res. *84*, 1583–1596.
166. Shi, Q., Zhu, Y., Ma, J., Chang, K., Ding, D., Bai, Y., Gao, K., Zhang, P., Mo, R., Feng, K., 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*, 1–14.
167. Moujaber, O., Mahboubi, H., Kodiha, M., Bouttier, M., Bednarz, K., Bakshi, R., White, J., Larose, L., Colmegna, I., and Stochaj, U. (2017). Dissecting the molecular mechanisms that impair stress granule formation in aging cells. Biochim. Biophys. Acta Mol. Cell Res. *1864*, 475–486.
168. Lian, X.J., and Gallouzi, I.-E. (2009). Oxidative Stress Increases the Number of Stress Granules in Senescent Cells and Triggers a Rapid Decrease in p21waf1/cip1 Translation. J. Biol. Chem. *284*, 8877–8887.
169. Omer, A., Patel, D., Lian, X.J., Sadek, J., Di Marco, S., Pause, A., Gorospe, M., and Gallouzi, I.E. (2018). Stress granules counteract senescence by sequestration of PAI-1. EMBO Rep. *19*, e44722.
170. Luo, T., Yang, S., Zhao, T., Zhu, H., Chen, C., Shi, X., Chen, D., Wang, K., Jiang, K., Xu, D., et al. (2023). Hepatocyte DDX3X protects against drug-induced acute liver injury via controlling stress granule formation and oxidative stress. Cell Death Dis. *14*, 400.
171. Park, Y.-J., Choi, D.W., Cho, S.W., Han, J., Yang, S., and Choi, C.Y. (2020). Stress Granule Formation Attenuates RACK1-Mediated Apoptotic Cell Death Induced by Morusin. Int. J. Mol. Sci. *21*, 5360.
172. Fujikawa, D., Nakamura, T., Yoshioka, D., Li, Z., Moriizumi, H., Taguchi, M., Tokai-Nishizumi, N., Kozuka-Hata, H., Oyama, M., and Takekawa, M. (2023). Stress granule formation inhibits stress-induced apoptosis by selectively sequestering executioner caspases. Curr. Biol. *33*, 1967–1981.e8.
173. Kim, W.J., Back, S.H., Kim, V., Ryu, I., and Jang, S.K. (2005). Sequestration of TRAF2 into stress granules interrupts tumor necrosis factor signaling under stress conditions. Mol. Cell Biol. *25*, 2450–2462.
174. Kesavardhana, S., Samir, P., Zheng, M., Malireddi, R.S., Karki, R., Sharma, B.R., Place, D.E., Briard, B., Vogel, P., and Kanneganti, T.D. (2021). DDX3X coordinates host defense against influenza virus by activating the NLRP3 inflammasome and type I interferon response. J. Biol. Chem. *296*.
175. Liu, Z., Rui, T., Lin, Z., Xie, S., Zhou, B., Fu, M., Mai, L., Zhu, C., Wu, G., and Wang, Y. (2022). Tumor-Associated Macrophages Promote Metastasis of Oral Squamous Cell Carcinoma via CCL13 Regulated by Stress Granule. Cancers *14*, 5081.
176. Wang, R., Cao, L., Thorne, R.F., Zhang, X.D., Li, J., Shao, F., Zhang, L., and Wu, M. (2021). LncRNA GIRGL drives CAPRIN1-mediated phase separation to suppress glutaminase-1 translation under glutamine deprivation. Sci. Adv. *7*, eabe5708.
177. Cereghetti, G., Wilson-Zbinden, C., Kissling, V.M., Diether, M., Arm, A., Yoo, H., Piazza, I., Saad, S., Picotti, P., Drummond, D.A., et al. (2021). Reversible amyloids of pyruvate kinase couple cell metabolism and stress granule disassembly. Nat. Cell Biol. *23*, 1085–1094.
178. Fonteneau, G., Redding, A., Hoag-Lee, H., Sim, E.S., Heinrich, S., Gaida, M.M., and Grabocka, E. (2022). Stress Granules Determine the Development of Obesity-Associated. Pancreatic Cancer. Cancer Discov. *12*, 1984–2005.
179. Amen, T., and Kaganovich, D. (2021). Stress granules inhibit fatty acid oxidation by modulating mitochondrial permeability. Cell Rep. *35*, 109237.
180. Wang, N., Li, T., Liu, W., Lin, J., Zhang, K., Li, Z., Huang, Y., Shi, Y., Xu, M., and Liu, X. (2023). USP7- and PRMT5-dependent G3BP2 stabilization drives de novo lipogenesis and tumorigenesis of HNSC. Cell Death Dis. *14*, 182.
181. Vinay, D.S., Ryan, E.P., Pawelec, G., Talib, W.H., Stagg, J., Elkord, E., Lichtor, T., Decker, W.K., Whelan, R.L., Kumara, H.M.C.S., et al. (2015). Immune evasion in cancer: Mechanistic basis and therapeutic

strategies. Semin. Cancer Biol. *35*, S185–S198.

182. Zhang, Y., Yue, C., Krichevsky, A.M., and Garkavtsev, I. (2024). Repression of the stress granule protein G3BP2 inhibits immune checkpoint molecule PD-L1. Mol. Oncol.. https://doi.org/10.1002/1878-0261.12915
183. Coelho, M.A., de Carné Trécesson, S., Rana, S., Zecchin, D., Moore, C., Molina-Arcas, M., East, P., Spencer-Dene, B., Nye, E., Barnouin, K., et al. (2017). Oncogenic RAS Signaling Promotes Tumor Immunoresistance by Stabilizing PD-L1 mRNA. Immunity *47*, 1083–1099.
184. Kim, D.J., Jang, J.H., Ham, S.Y., Choi, S.H., Park, S.S., Jeong, S.Y., Kim, B.C., Jeon, D.Y., Lee, B.J., Ko, B.K., et al. (2020). Doxorubicin inhibits PD-L1 expression by enhancing TTP-mediated decay of PD-L1 mRNA in cancer cells. Biochem. Biophys. Res. Commun. *522*, 402–407.
185. Yu, D., Tan, A.H.M., Hu, X., Athanasopoulos, V., Simpson, N., Silva, D.G., Hutloff, A., Giles, K.M., Leedman, P.J., Lam, K.P., et al. (2007). Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA. Nature *450*, 299–303.
186. Athanasopoulos, V., Barker, A., Yu, D., Tan, A.H.M., Srivastava, M., Contreras, N., Wang, J., Lam, K.P., Brown, S.H.J., Goodnow, C.C., et al. (2010). The ROQUIN family of proteins localizes to stress granules via the ROQ domain and binds target mRNAs. FEBS J. *277*, 2109–2127.
187. Glasmacher, E., Hoefig, K.P., Vogel, K.U., Rath, N., Du, L., Wolf, C., Kremmer, E., Wang, X., and Heissmeyer, V. (2010). Roquin binds inducible costimulator mRNA and effectors of mRNA decay to induce microRNA-independent post-transcriptional repression. Nat. Immunol. *11*, 725–733.
188. Franchini, D.M., Lanvin, O., Tosolini, M., Patras de Campaigno, E., Cammas, A., Péricart, S., Scarlata, C.M., Lebras, M., Rossi, C., Ligat, L., et al. (2019). Microtubule-Driven Stress Granule Dynamics Regulate Inhibitory Immune Checkpoint Expression in T Cells. Cell Rep. *26*, 94–107.e7.
189. Li, T., Zeng, Z., Fan, C., and Xiong, W. (2023). Role of stress granules in tumorigenesis and cancer therapy. Biochim. Biophys. Acta Rev. Canc *1878*, 189006.
190. Gao, X., Jiang, L., Gong, Y., Chen, X., Ying, M., Zhu, H., He, Q., Yang, B., and Cao, J. (2019). Stress granule: A promising target for cancer treatment. Br. J. Pharmacol. *176*, 4421–4433.
191. Adjibade, P., Simoneau, B., Ledoux, N., Gauthier, W.N., Nkurunziza, M., Khandjian, E.W., and Mazroui, R. (2020). Treatment of cancer cells with Lapatinib negatively regulates general translation and induces stress granules formation. PLoS One *15*, e0231894.
192. Vilas-Boas, F.d.A.S., da Silva, A.M., de Sousa, L.P., Lima, K.M., Vago, J.P., Bittencourt, L.F.F., Dantas, A.E., Gomes, D.A., Vilela, M.C., Teixeira, M.M., and Barcelos, L.S. (2016). Impairment of stress granule assembly via inhibition of the eIF2alpha phosphorylation sensitizes glioma cells to chemotherapeutic agents. J. Neuro Oncol. *127*, 253–260.
193. 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.
194. García, M.A., Carrasco, E., Aguilera, M., Alvarez, P., Rivas, C., Campos, J.M., Prados, J.C., Calleja, M.A., Esteban, M., Marchal, J.A., and Aránega, A. (2011). The chemotherapeutic drug 5-fluorouracil promotes PKR-mediated apoptosis in a p53-independent manner in colon and breast cancer cells. PLoS One *6*, e23887.
195. Li, H., Lin, P.H., Gupta, P., Li, X., Zhao, S.L., Zhou, X., Li, Z., Wei, S., Xu, L., Han, R., et al. (2021). MG53 suppresses tumor progression and stress granule formation by modulating G3BP2 activity in non-small cell lung cancer. Mol. Cancer *20*, 118.
196. Huang, G., Song, C., Wang, N., Qin, T., Sui, S., Obr, A., Zeng, L., Wood, T.L., Leroith, D., Li, M., and Wu, Y. (2020). RNA-binding protein CUGBP1 controls the differential INSR splicing in molecular subtypes of breast cancer cells and affects cell aggressiveness. Carcinogenesis *41*, 1294–1305.
197. Shi, X., Si, X., Zhang, E., Zang, R., Yang, N., Cheng, H., Zhang, Z., Pan, B., and Sun, Y. (2021). Paclitaxel-induced stress granules increase LINE-1 mRNA stability to promote drug resistance in breast cancer cells. J. Biomed. Res. *35*, 411–424.
198. Wang, R., Jiang, X., Bao, P., Qin, M., and Xu, J. (2019). Circadian control of stress granules by oscillating EIF2α. Cell Death Dis. *10*, 215.
199. Zhao, Z., Qing, Y., Dong, L., Han, L., Wu, D., Li, Y., Li, W., Xue, J., Zhou, K., Sun, M., et al. (2023). QKI shuttles internal m7G-modified transcripts into stress granules and modulates mRNA metabolism. Cell *186*, 3208–3226.e27.
200. Yang, T., Wang, G., Zhang, M., Hu, X., Li, Q., Yun, F., Xing, Y., Song, X., Zhang, H., Hu, G., and Qian, Y. (2023). Triggering endogenous Z-RNA sensing for anti-tumor therapy through ZBP1-dependent necroptosis. Cell Rep. *42*, 113377.
201. Moeller, B.J., Cao, Y., Li, C.Y., and Dewhirst, M.W. (2004). Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer Cell *5*, 429–441.
202. Freibaum, B.D., Messing, J., Nakamura, H., Yurtsever, U., Wu, J., Kim, H.J., Hixon, J., Lemieux, R.M., Duffner, J., Huynh, W., et al. (2024). Identification of small molecule inhibitors of G3BP-driven stress granule formation. J. Cell Biol. *223*, e202308083.
203. Seo, K.W., and Kleiner, R.E. (2023). Profiling dynamic RNA-protein interactions using small-molecule-induced RNA editing. Nat. Chem. Biol. *19*, 1361–1371.
204. An, T., Gong, Y., Li, X., Kong, L., Ma, P., Gong, L., Zhu, H., Yu, C., Liu, J., Zhou, H., et al. (2017). USP7 inhibitor P5091 inhibits Wnt signaling and colorectal tumor growth. Biochem. Pharmacol. *131*, 29–39.
205. Wu, C.T., Sheu, M.L., Tsai, K.S., Chiang, C.K., and Liu, S.H. (2011). Salubrinal, an eIF2α dephosphorylation inhibitor, enhances cisplatin-induced oxidative stress and nephrotoxicity in a mouse model. Free Radic. Biol. Med. *51*, 671–680.
206. Jeon, Y.-J., Kim, J.H., Shin, J.I., Jeong, M., Cho, J., and Lee, K. (2016). Salubrinal-Mediated Upregulation of eIF2α Phosphorylation Increases Doxorubicin Sensitivity in MCF-7/ADR Cells. Mol. Cell. *39*, 129–135.
207. Zyryanova, A.F., Kashiwagi, K., Rato, C., Harding, H.P., Crespillo-Casado, A., Perera, L.A., Sakamoto, A., Nishimoto, M., Yonemochi, M., Shirouzu, M., et al. (2021). ISRIB Blunts the Integrated Stress Response by Allosterically Antagonising the Inhibitory Effect of Phosphorylated eIF2 on eIF2B. Mol. Cell *81*, 88–103.e6.
208. Blanco, F.F., Preet, R., Aguado, A., Vishwakarma, V., Stevens, L.E., Vyas, A., Padhye, S., Xu, L., Weir, S.J., Anant, S., et al. (2016). Impact of HuR inhibition by the small molecule MS-444 on colorectal cancer cell tumorigenesis. Oncotarget *7*, 74043–74058.
209. Lang, M., Berry, D., Passecker, K., Mesteri, I., Bhuju, S., Ebner, F., Sedlyarov, V., Evstatiev, R., Dammann, K., Loy, A., et al. (2017). HuR Small-Molecule Inhibitor Elicits Differential Effects in Adenomatosis Polyposis and Colorectal Carcinogenesis. Cancer Res. *77*, 2424–2438.
210. Luvai, A., Mbagaya, W., Hall, A.S., and Barth, J.H. (2012). Rosuvastatin: a review of the pharmacology and clinical effectiveness in cardiovascular disease. Clin. Med. Insights Cardiol. *6*. CMC.S4324–S4324.
211. Xu, J.Z., Chai, Y.L., and Zhang, Y.L. (2016). Effect of rosuvastatin on high glucose-induced endoplasmic reticulum stress in human umbilical vein endothelial cells. Genet. Mol. Res. *15*.
212. Ferreira, P.M.P., Sousa, R.W.R.d., Ferreira, J.R.d.O., Militão, G.C.G., and Bezerra, D.P. (2021). Chloroquine and hydroxychloroquine in antitumor therapies based on autophagy-related mechanisms. Pharmacol. Res. *168*, 105582.
213. Attwood, K.M., Robichaud, A., Westhaver, L.P., Castle, E.L., Brandman, D.M., Balgi, A.D., Roberge, M., Colp, P., Croul, S., Kim, I., 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.
214. Adjibade, P., St-Sauveur, V.G., Quevillon Huberdeau, M., Fournier, M.J., Savard, A., Coudert, L., Khandjian, E.W., and Mazroui, R. (2015). Sorafenib, a multikinase inhibitor, induces formation of stress granules in hepatocarcinoma cells. Oncotarget *6*, 43927–43943.
215. Tong, F., Hu, H., Xu, Y., Zhou, Y., Xie, R., Lei, T., Du, Y., Yang, W., He, S., Huang, Y., et al. (2023). Hollow copper sulfide nanoparticles carrying ISRIB for the sensitized photothermal therapy of breast cancer and brain metastases through inhibiting stress granule formation and reprogramming tumor-associated macrophages. Acta Pharm. Sin. B *13*, 3471–3488.
216. Yao, R.Q., Ren, C., Xia, Z.F., and Yao, Y.M. (2021). Organelle-specific autophagy in inflammatory diseases: a potential therapeutic target underlying the quality control of multiple organelles. Autophagy *17*, 385–401.
217. Ryan, L., and Rubinsztein, D.C. (2024). The autophagy of stress granules. FEBS Lett. *598*, 59–72.
218. Morisaki, T., and Stasevich, T.J. (2022). Single-Molecule Imaging of mRNA

Interactions with Stress Granules. Methods Mol. Biol. *2428*, 349–360.

219. Hoerth, K., Eiermann, N., Beneke, J., Erfle, H., and Stoecklin, G. (2022). Image-Based Screening for Stress Granule Regulators. Methods Mol. Biol. *2428*, 361–379.

220. Freibaum, B.D., Messing, J., Yang, P., Kim, H.J., and Taylor, J.P. (2021). High-fidelity reconstitution of stress granules and nucleoli in mammalian cellular lysate. J. Cell Biol. *220*, e202009079.

221. Martin, S., and Tazi, J. (2014). Visualization of G3BP stress granules dynamics in live primary cells. J. Vis. Exp. *51197*, 51197. https://doi.org/10.3791/51197.

222. Kochan, J., and Wawro, M. (2024). Immunofluorescence Combined with Single-Molecule RNA Fluorescence In Situ Hybridization for Concurrent Detection of Proteins and Transcripts in Stress Granules. Methods Mol. Biol. *2752*, 127–141.

223. Kedersha, N., Tisdale, S., Hickman, T., and Anderson, P. (2008). Real-time and quantitative imaging of mammalian stress granules and processing bodies. Methods Enzymol. *448*, 521–552.