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Stress Granules in Cancer

Min-Seok Song,
Elda Grabocka
Department of Cancer Biology, Thomas Jefferson University, Philadelphia, PA, USA

Abstract

The capacity of cells to organize complex biochemical reactions in intracellular space is a fundamental organizational principle of life. Key to this organization is the compartmentalization of the cytoplasm into distinct organelles, which is frequently achieved through intracellular membranes. Recent evidence, however, has added a new layer of flexibility to cellular compartmentalization. As such, in response to specific stimuli, liquid-liquid phase separations can lead to the rapid rearrangements of the cytoplasm to form membraneless organelles. Stress granules (SGs) are one such type of organelle that form specifically when cells are faced with stress stimuli, to aid cells in coping with stress. Inherently, altered SG formation has been linked to the pathogenesis of diseases associated with stress and inflammatory conditions, including cancer. Exciting discoveries have indicated an intimate link between SGs and tumorigenesis. Several pro-tumorigenic signaling molecules including the RAS oncogene, mTOR, and histone deacetylase 6 (HDAC6) have been shown to upregulate SG formation. Based on these studies, SGs have emerged as structures that can integrate oncogenic signaling and tumor-associated stress stimuli to enhance cancer cell fitness. In addition, growing evidence over the past decade suggests that SGs function not only to regulate the switch between survival and cell death, but also contribute to cancer cell proliferation, invasion, metastasis, and drug resistance. Although much remains to be learned about the role of SGs in tumorigenesis, these studies highlight SGs as a key regulatory hub in cancer and a promising therapeutic target.

Keywords

Cancer; Membraneless organelles; Stress adaptation; Stress granules

1 Introduction

Stress granules (SGs) are non-membranous cytoplasmic organelles that assemble when cells are exposed to stress (Buchan and Parker 2009; Kedersha et al. 2013; Buchan 2014). They consist of a vast proteomic and transcriptomic network and range in size from tens of nanometers to several micrometers (Anderson and Kedersha 2008; Jain et al. 2016; Protter and Parker 2016; Khong et al. 2017; Namkoong et al. 2018). These structures are highly dynamic and can undergo fusion and fission. Furthermore, once stress subsides,

(✉)E. Grabocka, Elda.Grabocka@jefferson.edu.
Min-Seok Song and Elda Grabocka contributed equally to this work.

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SGs disassemble, and their components disperse back into the cytosol (Protter and Parker 2016; Wheeler et al. 2016). Earlier reports proposed that SGs function to store and target mRNA for degradation during stress (Anderson and Kedersha 2008). Studies over the past decade, however, have drastically expanded our understanding of their function. It is now well-established that SGs function as signaling hubs that regulate gene expression and signal transduction, and are critical to the cellular stress response and survival under adverse conditions.

In vivo, SGs have been associated with several pathologies, including cancer (Grabocka and Bar-Sagi 2016; Cruz et al. 2019; Herman et al. 2019; Wolozin and Ivanov 2019). Studies in cancer cells and animal models of tumorigenesis have established SGs as a stress-adaptive strategy hijacked by cancer cells to support tumorigenesis (Somasekharan et al. 2015; Grabocka and Bar-Sagi 2016; Protter and Parker 2016). Stress adaptation is emerging as an important property of cancer cells (Sharma et al. 2016; Truitt and Ruggero 2016; El-Naggar and Sorensen 2018). As oncogenic-driven hyperproliferation demands a high expenditure of cellular resources, cancer cells are often faced with stress conditions (Solimini et al. 2007; Stylianopoulos et al. 2012; Urra et al. 2016). As such, the increased demand for protein synthesis and flux in the endoplasmic reticulum results in proteotoxic stress and misfolded proteins, and hyper-replication of DNA leads to DNA damage and genotoxic stress (Joyce and Pollard 2009; Fiaschi and Chiarugi 2012; Yadav et al. 2014; Anastasiou 2017; Gouirand et al. 2018). The increased metabolic demand contributes to nutrient stress, reactive oxidant species (ROS), and pH imbalances (Vincent et al. 2015; Panieri and Santoro 2016). Furthermore, as tumors outgrow the local vascularization, the inadequate blood supply leads to reduced oxygen and nutrient levels (Fig. 1) (Wellen and Thompson 2010; Semenza 2012). Such levels of stress would normally lead to cell death, but cancer cells are able to quickly adapt and survive (Wellen and Thompson 2010; Gorrini et al. 2013; Wang and Kaufman 2014; Senft and Ronai 2016; Lee et al. 2020). Stress adaptation, therefore, can contribute to tumorigenesis by enhancing the cellular fitness and supporting the survival of cancer cells.

The stress adaptation of cancer cells is conferred, in large part, by the capacity of oncogenic molecules to elicit compensatory responses to tumor-associated stresses in order to promote tumor cell survival (Solimini et al. 2007; Commisso et al. 2013; Ruggero 2013; Easwaran et al. 2014; Eirew et al. 2015; Perera et al. 2015; Amaravadi et al. 2016; Lee et al. 2020). Such responses include alterations to the genetic, epigenetic, and transcriptomic landscape and, more recently, the hijacking of stress-coping cellular processes. Examples of the latter include oncogene-induced upregulation of macropinocytosis and autophagy, as well as modifications of lysosomes, which enable cancer cells to cope with nutritional stress (Commisso et al. 2013; Perera et al. 2015; Amaravadi et al. 2016). In addition, cancer cells upregulate the unfolded protein response (UPR) to cope with ER stress and misfolded proteins (Obacz et al. 2017). Whereas these processes are upregulated by cancer cells to cope with specific stress stimuli, SGs have been identified as a cancer cell stress-adaptive mechanism for a broad spectrum of tumor-associated stresses including oxidative-, proteotoxic-, osmotic- stress, as well as for nutrient deprivation (Fig. 1) (Somasekharan et al. 2015; Grabocka and Bar-Sagi 2016; Protter and Parker 2016).

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Several studies have demonstrated that pro-tumorigenic signaling pathways that are hyperactivated in cancer stimulate the formation of SGs (Somasekharan et al. 2015; Grabocka and Bar-Sagi 2016; Protter and Parker 2016). This enhanced formation of SGs, in turn, may promote cancer development and progression. Evidence exists that SGs may support tumorigenesis not only through facilitating cancer cell survival but also through contributing to tumor cell proliferation and metastasis (Fig. 1). In addition, it has been shown that SGs may play an important role in the development of drug resistance (Fig. 1). These studies highlight that while SGs are important in the normal cellular stress response and may impact several diseases (reviewed in excellent detail elsewhere (Protter and Parker 2016; Mahboubi and Stochaj 2017; Cruz et al. 2019; Herman et al. 2019; Wolozin and Ivanov 2019)), the hijacking of this process by cancer cells may be critical for tumorigenesis and a promising therapeutic target. Here we review recent data illuminating the oncogenic signaling pathways that promote the formation of SGs in cancer cells and the mechanisms through which SGs may contribute to tumor progression and response to chemotherapy. In addition, we discuss how leveraging this knowledge may instruct the development of therapeutic strategies for the treatment of cancer and overcoming drug resistance.

2 Properties of Stress Granules

2.1 Formation of Stress Granules

Since the initial discovery of SGs in tomato cells exposed to heat shock, several studies have revealed SG formation as an evolutionary conserved response to stress produced by plants, protozoa, yeast, *C. elegans*, *Drosophila*, and mammalian cells (Nover et al. 1983; Arrigo et al. 1988; Collier et al. 1988; Buchan et al. 2008; Farny et al. 2009; Thomas et al. 2011; Gutierrez-Beltran et al. 2015). SG formation is induced by a variety of stress stimuli including oxidative stress, heat shock, ER stress, nutrient deprivation, UV irradiation, proteotoxic stress, and several chemotherapeutic agents (Kedersha et al. 1999; Kimball et al. 2003; Kwon et al. 2007; Mazroui et al. 2007; Fournier et al. 2010; Emara et al. 2012; Kaehler et al. 2014; Moutaoufik et al. 2014; Adjibade et al. 2015; Grabocka and Bar-Sagi 2016; Reineke et al. 2018; Lin et al. 2019).

The formation of SGs is closely linked to translation inhibition (Kedersha et al. 1999; Protter and Parker 2016). Cells respond to stress by blocking protein synthesis via the phosphorylation of the α subunit of the eukaryotic initiation factor 2 (eIF2). In mammalian cells, the phosphorylation of eIF2α is mediated by a family of four different serine/threonine kinases each of which is activated by specific forms of stress. These kinases include the general control non-derepressible 2 (GCN2) kinase which is activated by amino acid deprivation; the heme-regulated inhibitor (HRI) kinase which is activated by oxidative or osmotic stress; the double stranded RNA-dependent protein (PKR) kinase which is activated in response to viral infections; and the PKR-like endoplasmic reticulum kinase (PERK) which is activated by ER stress (Wek et al. 2006; Donnelly et al. 2013). eIF2α is one of the three subunits (α, β, γ) of eIF2 which mediates the binding of initiator methionyl-tRNA (Met-$tRNA_i^{Met}$) to the ribosome in a GTP-dependent manner (Donnelly et al. 2013). The eIF2-Met-$tRNA_i^{Met}$-GTP complex binds the 40S ribosomal subunit, as well as eIF1, eIF1A, eIF5, and eIF3, to form the 43S pre-initiation complex (PIC); PIC then associates

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with eIF4F on mRNA to form a new 48S complex which scans the mRNA for the start codon (AUG). Phosphorylation of eIF2α under stress prevents the formation of eIF2- Met-$tRNA_i^{Met}$-GTP, thus resulting in a translationally stalled, noncanonical 48S complex that is unable to recruit the 60S ribosomal subunit (Jackson et al. 2010). Consequently, ribosomes runoff the transcripts, causing a flux of messenger ribonucleoprotein complexes (mRNPs) and exposed RNA, which are critical for SG formation (Wheeler et al. 2016).

It is important to note that while translation inhibition is key for the formation of SGs, it can also occur independently of eIF2α phosphorylation (Jackson et al. 2010). For one, changes in the composition or activity of the eIF4F-cap binding complex (eIF4A, eIF4E, eIF4G) can inhibit translation and induce SG formation. As such, hydrogen peroxide initiates SG assembly by inhibiting translation initiation through disrupting the interaction of eIF4E with eIF4G (Emara et al. 2012; Fujimura et al. 2012). Also, chemicals such as hippuristanol and pateamine A interfere with translation initiation by blocking the eIF4A helicase, which is required for the ribosome recruitment phase of translation initiation. Lastly, the anti-inflammatory lipids 15-deoxy- -12,14-prostaglandin J2 and prostaglandin A1, which are potent inducers of SG formation, inhibit translation by preventing the association of eIF4A with eIF4G (Bordeleau et al. 2006; Dang et al. 2006; Kim et al. 2007; Grabocka and Bar-Sagi 2016).

Regardless of the mode of translation inhibition, the resulting flux of mRNPs and exposed RNA are essential for the formation of SGs (Protter and Parker 2016; Wheeler et al. 2016; Ivanov et al. 2019). These molecules initiate the first steps of SG assembly by binding to RNA-binding proteins termed SG-nucleating proteins, which include the poly(A)-binding protein (PABP1) PABP1, the T-cell internal antigen 1 (TIA-1), TIA-1 related (TIAR), and Ras-GTPase-activating protein SH3-domain-binding protein1 (G3BP1). SG assembly is further aided by the ability of SG-nucleating proteins to phase-separate and coalesce in the cytoplasm, leading to the formation of nascent SGs. Further recruitment of proteins and transcripts via protein-protein, protein-RNA, and RNA-RNA interactions results in the formation of mature SGs. The phase-separation capacity of SG-nucleating proteins is mediated by intrinsically disordered domains (IDD), which are a prominent feature of SG-nucleator proteins (Protter and Parker 2016; Mahboubi and Stochaj 2017). The role of these domains in the coalescence of SG-nucleator proteins is supported by several studies showing that, at high concentration, IDD domains can induce spontaneous phase separation. In agreement with this notion, one study showed that overexpression of SG nucleators, which would presumably increase the concentration of IDD domains, is sufficient to induce SG formation in vitro even in the absence of stress (Gilks et al. 2004; Matsuki et al. 2013; Lin et al. 2015; Molliex et al. 2015). In addition to IDD domains, phase separation of SG nucleators is regulated by posttranslational modifications which can enhance or weaken the multivalent interactions between these molecules (Kwon et al. 2007; Tsai et al. 2008; Carpio et al. 2010; Xie and Denman 2011; Owen and Shewmaker 2019). Shedding further light onto the macromolecular interactions that contribute to SG assembly, a recent study indicated that RNA-RNA interactions and ability to self-coalesce wherever there is a high concentration of RNA may also contribute to SG assembly (Van Treeck et al. 2018). Taken together, these features support a model where SGs are formed by the concerted action of phase separation, protein-RNA, protein-protein, and RNA-RNA interactions.

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2.2 Stress Granule Structure

SGs are non-membranous structures of the cytoplasm that contain stalled mRNA transcripts, poly(A) mRNAs, microRNAs, translation initiation factors, large and small ribosomal subunit protein components, and a vast network of proteins (Jain et al. 2016; Khong et al. 2017; Markmiller et al. 2018; Namkoong et al. 2018). Recent studies suggest that SGs have a biphasic architecture consisting of a stable core, which is surrounded by a dynamic shell (Fujimura et al. 2009; Souquere et al. 2009; Jain et al. 2016; Wheeler et al. 2016; Markmiller et al. 2018). This architecture is thought to provide multiple levels of functionality within SGs whereby the shell provides a platform for an active exchange of transcripts and protein with the cytoplasm, whereas compartmentalization to the stable core by definition allows for more stable retention (Jain et al. 2016; Protter and Parker 2016; Wheeler et al. 2016; Van Treeck et al. 2018).

The dynamic nature of SG shells has rendered their full isolation and characterization intractable to date. However, stable SG cores have been purified and reveal a vast network of 411 proteins (Jain et al. 2016). These include several RNA-binding proteins, an array of signaling proteins including protein kinases, phosphatases, GTPases, ATPases, adaptor proteins, endoribonucleases, helicases, glycosyltransferases, ubiquitin modifying enzymes, and components of the RNAi machinery (Jain et al. 2016). Building on the methodology of Jain et al., characterization of the SG-core transcriptome revealed that 10–12% of the total mRNA molecules accumulate in SGs (Khong et al. 2017; Namkoong et al. 2018; Matheny et al. 2019). This recruitment does not appear to be random. The ~185 gene mRNA transcripts that have been identified as most likely to find their way to SGs follow patterns of shared transcript length and translation efficiency and share a handful of specific RNA motifs (Khong et al. 2017; Namkoong et al. 2018; Matheny et al. 2019). Longer mRNAs and ncRNAs, transcripts with lower translation efficiency, and transcripts with RNA sequence motifs such as adenylate-uridylate (AU)-rich element, Pumilio-binding element, and guanylate-cytidylate (GC)-rich element are highly common in SGs (Lin et al. 2007; Khong et al. 2017; Namkoong et al. 2018; Van Treeck et al. 2018; Matheny et al. 2019; Moon et al. 2019). While SG cores induced by different stimuli shared several protein and transcript components, considerable differences were also observed, depending on the specific type of stress (Khong et al. 2017; Namkoong et al. 2018). Thus, the composition of SG cores is specific to the type of stress. Research has yet to illuminate exactly which proteins and transcripts associate with the SG shells, but it is likely that similar to SG cores, they will capture, modify, and exchange proteins and transcripts based on the specific kind of stress that the cell is experiencing.

3 Dysregulated Cancer Signaling and Stress Granule Formation

In vivo, SGs are found in cancer cells of osteosarcomas and tumors of the pancreas and colon but are absent in normal cells from the same tissues (Somasekharan et al. 2015; Grabocka and Bar-Sagi 2016). As previously mentioned, tumors are frequently faced with stress conditions, and perhaps not surprisingly, SGs are often detected in tumor regions experiencing stress. Evidence suggests, however, that the presence of SGs in tumors is not a sole consequence of heightened stress stimuli, but that dysregulation of several

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signaling pathways also contributes to SG formation. Dysregulated cancer signaling appears to facilitate SG formation in response to stress through promoting translation inhibition and protein-protein interactions important for SG assembly. This section discusses how dysregulated RAS, mTOR, HDAC, glycolytic, and hexosamine biosynthetic pathways can promote SG formation in cancer cells in vitro and in vivo.

3.1 RAS

Mutations in the *RAS* genes (*KRAS*, *NRAS*, and *HRAS*) constitute one of the largest oncogenic alterations in cancer and are present in approximately 30% of all human cancers (Pylayeva-Gupta et al. 2011). Mutant RAS proteins drive several cell functions that support cancer development and progression including cancer cell proliferation, apoptosis, metastasis, metabolism, immune modulation, cancer-associated fibroblast modulation, and ECM composition and structure modification (Liu et al. 2011; Tao et al. 2014; Dias Carvalho et al. 2018; Yang et al. 2018). Furthermore, accumulating evidence indicates that mutant RAS proteins stimulate stress-adaptive responses, allowing the cell to resist tumor-associated stresses and chemotherapeutic agents (Commisso et al. 2013; Tao et al. 2014; Amaravadi et al. 2016; Yang et al. 2018).

SGs were observed in mutant KRAS pancreatic cancer cells but not in normal pancreas tissue, in both human samples and mouse models of pancreatic cancer (Grabocka and Bar-Sagi 2016). As SGs in this setting were detected in the absence of exogenous stress stimuli, but were present in hypoxic tumor regions, this study first linked SG formation with tumor-associated stresses in vivo. Moreover, the study showed that SGs were present in mutant KRAS pancreatic tumors but not in wild-type (WT) RAS tumors, despite similar levels of hypoxia. This observation indicates a cooperation between mutant KRAS signaling and tumor-associated stresses in SG formation. Of note, SGs were also detected in non-hypoxic regions of mutant KRAS pancreatic tumors, suggesting that mutant KRAS may cooperate with additional stresses in stimulating SG formation. Consistent with this model, mutant KRAS enhanced SG formation in cells exposed to various forms of stress in vitro. These included oxidative stress, proteotoxic stress, UV-C irradiation, and chemotherapeutic agent-induced stress. Mutant KRAS cells also showed a heightened dependence on SGs for survival under stress stimuli, when compared to KRAS-WT cancer cells (Grabocka and Bar-Sagi 2016). As such, inhibition of SG formation in KRAS mutant cells led to higher levels of cell death compared to KRAS-WT cells. Thus, higher cellular levels of SGs may indicate a heightened dependence on SGs for cancer cell survival. An earlier study reported that overexpression of mutant HRAS also stimulated SG formation thus suggesting that all mutant Ras isoforms may be able to stimulate SGs in vivo (Tourriere et al. 2003). With all of this in mind, SGs may be a unique vulnerability that can be exploited for the treatment of all *RAS* mutant tumors, the treatment options for which are currently limited.

Mechanistically, mutant KRAS was shown to stimulate SG formation by enhancing the levels of the prostaglandin 15-deoxy-delta 12,14-prostaglandin J2 (15-d-PGJ2) (Fig. 2) (Grabocka and Bar-Sagi 2016). 15-d-PGJ2 can induce SG formation by inhibiting translation through covalently binding to eIF4A to block its interaction with eIF4G, as well as stimulating eIF2α phosphorylation (Kim et al. 2007; Tauber and Parker 2019). Recently,

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the nuclear factor erythroid 2-related factor 2 (NRF2) was also implicated in 15-d-PGJ2-mediated SG formation in KRAS mutant pancreatic cancer cells (Mukhopadhyay et al. 2020). The mechanisms through which 15-d-PGJ2-stimulated NRF2 promotes SG formation remain unclear. However, NRF2 regulation of SGs was shown to rely on glutamine, thereby linking KRAS-mediated SG induction to glutamine metabolism.

Mutant KRAS was shown to stimulate 15-d-PGJ2 production through the downstream effector molecules RAF and RALGDS (Grabocka and Bar-Sagi 2016). Signaling from these KRAS effector molecules upregulates15-d-PGJ2 through two different paths. For one, mutant KRAS signaling upregulates cyclooxygenase 2 (COX2), which catalyzes 15-d-PGJ2 synthesis. Secondly, mutant KRAS downregulates the NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (HPGD), which inhibits prostaglandin catabolism.

Interestingly, 15-d-PGJ2 is also secreted from mutant KRAS cancer cells to stimulate SG formation in a paracrine manner (Grabocka and Bar-Sagi 2016). In addition, paracrine stimulation of SG formation by mutant KRAS cancer cells promoted the survival of KRAS-WT cells when exposed to stress stimuli. The observation that mutant KRAS cells can promote survival of KRAS-WT cells through paracrine induction of SG formation is important; it raises the possibility that SG formation serves as a platform for mutant KRAS to promote the stress resistance and survival of the various cell types in the tumor stroma. Coupling this idea with the well-established role of tumor stroma in the development, growth, and drug resistance of mutant KRAS tumors, these findings also highlight the need for a better understanding of how SGs are integrated in KRAS-driven tumorigenesis.

3.2 mTORC1

The mammalian target of rapamycin (mTOR) is a crucial signaling node that regulates cell survival, proliferation, and metabolism (Saxton and Sabatini 2017; Mossmann et al. 2018). mTOR operates in two multi-protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) which have distinct compositions, functions, and substrate specificities. Both mTORC1 and mTORC2 are commonly hyperactivated in cancer; however, only mTORC1 activity has been linked to SG formation in cancer cells (Guertin and Sabatini 2007). mTORC1 is considered to be an essential factor for cancer metabolism reprogramming and adaptation to cellular stress (Chantranupong et al. 2016; Wolfson et al. 2016; Harachi et al. 2018; Lee et al. 2018). The mTORC1 catalytic complex consists of mTOR and co-factor molecules which include regulatory-associated protein of mTOR (RAPTOR), DEP domain containing mTOR interacting protein (DEPTOR) proline-rich AKT substrate 40 kDa (PRAS-40), FKBP38, and mammalian lethal with Sec13 protein 8 (mLST8). mTORC1 activity is both positively and negatively regulated by components of the catalytic complex.

Several studies have shown that mTORC1 activation in cancer cells can facilitate SG formation (Fig. 2). Inhibition of mTORC1, either genetically through shRNA-mediated downregulation or through pharmacological inhibition of its catalytic activity, impairs SG formation in cancer cells exposed to oxidative or proteotoxic stress (Fournier et al. 2013; Wippich et al. 2013). Similarly, inhibition of mTORC1 activity through the downregulation of RAPTOR also impaired SG formation (Fournier et al. 2013). Furthermore, mTORC1

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inhibition impaired the activations of SG-mediated anti-apoptotic pathways under stress conditions (Fournier et al. 2013; Wippich et al. 2013).

While the mechanistic pathways through which mTORC1 facilitates SG formation have not been fully elucidated, two major downstream effector molecules, the ribosomal protein S6 kinase 1 and 2 (S6K1, S6K2) and the eukaryotic translation initiation factor 4E (eIF4E) binding protein 1 (4EBP1), have been implicated (Fournier et al. 2013; Sfakianos et al. 2018). Both S6K1 and S6K2 were shown to localize to SGs, and their kinase activity was required for SG formation under conditions of oxidative stress (Sfakianos et al. 2018). Interestingly, S6K1 and S6K2 appear to play distinct roles in SG formation. S6K1 was shown to promote the formation of SGs by regulating eIF2α phosphorylation, whereas S6K2 was required for SG maintenance after assembly (Sfakianos et al. 2018). mTORC1-stimulated 4EBP1 has also been implicated in SG formation under oxidative stress conditions (Fig. 2). In contrast to mTORC1-S6K1 mediated SG formation, the formation of SGs via mTORC1-4EBP1 appears to be peIF2α independent (Fournier et al. 2013). Instead, mTORC1-4EBP1 is thought to promote SGs by impinging on the eIF4E-eIF4GI interaction and translation initiation under stress.

It is somewhat paradoxical for a pathway that is best known for stimulating protein translation to be associated with translation inhibition. A potential explanation may be that under specific stress stimuli, mTORC1 promotes SG formation independent of its effect on protein synthesis. In this context, activation of stress kinases would counter mTORC1 signaling and inhibit translation; this would initiate SG formation which is then aided by the capacity of mTORC1 to promote protein interactions and modifications with roles in SG formation. Once components of the mTORC1 complex and effector molecules are recruited to SGs however, mTORC1 would be prevented from stimulating translation in the cytosolic compartment. In agreement with this model, SGs have been shown to inhibit mTORC1 activity (Thedieck et al. 2013; Wippich et al. 2013). This is consistent with studies showing that while mTORC1 activation is required for cancer cell survival, chronic hyper-active mTORC1 can lead to apoptosis (Wippich et al. 2013). Thus, by recruiting mTORC1 and inhibiting its cytosolic function, SGs would contribute to cell survival by blunting chronic hyperactivation of mTORC1 (Wippich et al. 2013).

Mechanistically, SGs restrict mTORC1 hyperactivation through sequestering components of the catalytic complex including mTOR and RAPTOR and all three subunits (α-catalytic subunit; β and γ- regulatory subunits) of the upstream activator AMP-activated protein serine/threonine protein kinase (AMPK) (Hofmann et al. 2012; Takahara and Maeda 2012; Thedieck et al. 2013; Wippich et al. 2013). Distinct from mTOR and RAPTOR however, inhibition of AMPK does not impair SG formation in cancer cells. These studies have suggested that AMPK recruitment via interaction with G3BP1 occurs in the later stages of SG formation as a potential mechanism to restrain mTORC1 hyperactivation and promote survival.

Notably, the reactivation of mTORC1 in the recovery phase after stress has subsided has also been linked to SGs. As such, SG disassembly was shown to contribute to the activation of mTORC1 by the dual specificity tyrosinephosphorylation-regulated kinase 3

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(DYRK3) (Wippich et al. 2013). In its inactive state, DYRK3 promotes SG formation and, consequently, the recruitment of mTOR to SGs and inhibition of mTORC1. Stress recovery is associated with DYRK3 activation which stimulates SG dissolution to release mTORC1 components while simultaneously phosphorylating and inhibiting the mTORC1 inhibitor PRAS40. Altogether, these studies indicate that SG formation contributes to the inactivation of mTORC1 during oxidative stress, whereas SG dissolution contributes to the necessary reactivation during stress recovery.

3.3 Glycolysis and the Hexosamine Biosynthetic Pathway

It is well established that cancer cells alter their metabolism to derive energy from glycolysis instead of mitochondrial oxidative phosphorylation and utilize more glucose than normal cells (Ganapathy-Kanniappan and Geschwind 2013; Pavlova and Thompson 2016). Whereas the majority of glucose that enters the cell proceeds to glycolysis for ATP generation, the remaining glucose enters the hexosamine biosynthetic pathway (HBP) and along with glutamine, glucosamine, and acetylcoenzyme A is utilized to generate the amino sugar uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) (Akella et al. 2019). Both glycolysis and the HBP pathway are known to promote SG formation, indicating that enhanced glycolytic and HBP flux may contribute to the formation of SGs observed in tumors (Fig. 2) (Jain et al. 2016).

A proteomic analysis of mammalian stress granule cores in cancer cells revealed a large number of proteins with ATPase activity as components of SGs (Jain et al. 2016). This study also showed that ATP is required for both SG assembly and dynamics. Whether specific ATPases are required for these processes remains to be elucidated (Jain et al. 2016). However, given that cancer cells have a preferential reliance on glycolysis for ATP production, inhibition of glycolysis might be expected to impair SG formation in cancer cells. This prediction is supported by evidence that blocking the glycolytic pathway impaired SG formation in sarcoma cells (Jain et al. 2016). Glycolytic inhibitors, therefore, may be a promising strategy to inhibit SGs in vivo.

The final product of the HBP pathways, UDP-GlcNAc, is critical for the generation of metabolic intermediates as well as for the glycosylation of proteins; UDP aids in the N-linked and O-linked glycosylation of proteins in the ER and Golgi and in the O-Linked N-Acetylglucosamine (O-GlcNAc) modification of nuclear and cytoplasmic proteins by OGT (O-GlcNAc transferase) (Akella et al. 2019). Several studies support a role for glycosylation in tumorigenesis, and changes in protein glycosylation have been observed in several cancers including those of the pancreas, colon, melanoma, lung, liver, and prostate (Sharma et al. 2016). One proposed mechanism through which altered protein glycosylation contributes to cancer progression is through enabling cancer cells to cope with stress. Stress stimuli have been shown to enhance protein O-GlcNAc modifications, and oncogenic pathways such as PI3K-mTOR-MYC and MEK/ERK signaling pathways can stimulate OGT activity and O-GlcNAc modifications to enhance cell survival under stress (Sohn et al. 2004; Zachara et al. 2004; Taylor et al. 2008; Ferrer et al. 2014; Sodi et al. 2015; Zhang et al. 2015; Katai et al. 2016).

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An RNA-mediated interference-based screen in osteosarcoma cells identified the HBP pathway and O-GlcNAc protein modifications as critical to SG formation, thereby implicating SGs as a potential mechanism through which enhanced HBP flux promotes tumorigenesis (Ohn et al. 2008). Knockdown of either sortilin (trans-membrane protein that regulates the vesicular transport of the GLUT4 glucose transporter and glucose uptake), GFAT2 (glutamine: fructose 6 phosphate amidotransferase 2), or OGT inhibited SG formation in cancer cells but had no effect on eIF2α phosphorylation. Thus, the HBP pathway acts independently of peIF2α in inducing SGs in cancer cells. Instead, HBP-dependent SG formation is mediated by O-GlcNAc modification of receptor for activated C kinase 1 (RACK1), PROHIBITIN-2, and several ribosomal proteins, which promotes their aggregation into SGs (Ohn et al. 2008). In addition to components of the translational machinery, the HBP pathway regulates multiple proteins with established roles in SG formation (mTOR and AMPK) and can be manipulated by endogenous metabolites (glutamine) and oncogenic signaling pathways implicated in SG formation (PI3K and RAS/RAF). It remains to be elucidated how these signals integrate in vivo to promote SG upregulation. Nonetheless, given the role of the HBP pathway in SG formation, it is a promising therapeutic target for inhibiting SG formation in cancer.

3.4 HDAC6

Histone acetylation and deacetylation is an important posttranslational mechanism that regulates gene expression. Histone deacetylase (HDAC) proteins are key enzymes that regulate acetylation levels. Within the HDAC family, HDAC6 is unique as it determines the acetylation status of not only histones but also of several non-histone substrates such as dynein, α-tubulin, cortactin, and HSP90 (Li et al. 2018). HDAC6 is overexpressed in melanoma, lung, pancreas, breast, and bladder cancer and is thought to promote tumorigenesis by regulating cancer cell proliferation, metastasis, and immune regulators through both its histone and non-histone substrates (Lee et al. 2008; Wickstrom et al. 2010; Lafarga et al. 2012; Woan et al. 2015; Li et al. 2018). HDAC6 was shown to be a stable integral component of SGs and critical to SG formation in cancer cells under various stress stimuli including oxidative stress, UV irradiation, mitochondrial stress, or heat shock (Kwon et al. 2007). Mechanistically, HDAC6 is thought to promote SG formation through deacetylating G3BP1 which stimulates its RNA-dependent interaction with PABP1, a key component and regulator of SG assembly (Fig. 2) (Gal et al. 2019). In addition, the interaction of HDAC6 with dynein and microtubules has also been suggested to promote SG formation, potentially through mediating mRNP translocation to SGs (Kwon et al. 2007).

4 Stress Granules and Cancer Hallmarks

Significant amount of evidence supports a role for SGs in tumorigenesis. However, the cancer hallmarks impacted by SGs, and the mechanisms through which they do so, remain to be fully understood. This section discusses the role of SGs in the pathogenesis of cancer and the evidence linking SGs to cancer cell proliferation, metastasis, and survival and chemotherapy resistance.

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4.1 Stress Granules and Proliferation

Accumulating evidence indicates that SG formation is linked to the proliferative status of cells. One such example is cellular senescence, which has been shown to have a profound effect on the cellular capacity to form SGs. Cellular senescence is a cytostatic program that can be triggered by multiple mechanisms. These include (a) telomere attrition that occurs with replicative “aging” of cells – known as replicative senescence – and (b) exposure to exogenous agents that induce DNA damage (oxidative stress, chemotherapy, UV light), which is referred to as stress-induced premature senescence and leads to cell-cycle arrest via the activation of the DNA damage response (DDR). Lastly, acquisition of oncogenic mutations can lead to oncogene-induced senescence, which can also be mediated by DDR (Campisi and d’Adda di Fagagna 2007; Campisi 2013).

As a cell cycle-arrest program, senescence functions as a tumor-suppressive mechanism. However, senescent cells can also contribute to the generation of a tumor-promoting microenvironment via the secretion of several cytokines and chemokines (senescence-associated secretory phenotype; SASP) that promote cell cycle progression, de-differentiation, and metastasis. In in vitro models of stress-induced premature senescence, transition from the proliferative state to pre-senescence and senescence correlated with a progressive impairment of the cellular capacity to form SGs (Lian and Gallouzi 2009; Moujaber et al. 2017; Omer et al. 2018). These observations raised the possibility that SGs may play a role in preventing cells from exiting cell cycle and entering senescence. Mechanistically, senescence-dependent SG impairment was shown to be driven by the depletion of the transcription factor specific protein 1 (SP1) which regulates the expression of the SG-nucleating proteins G3BP1, TIA-1/TIAR, eIF4G, hnRNPK, and HuR (Moujaber et al. 2017). Consistent with a role for SGs in inhibiting senescence, a study showed SG inhibition via G3BP1 knockdown promoted stress-induced cellular senescence (Omer et al. 2018). SGs therefore appear to inhibit cellular senescence, while acquisition of the senescent phenotype on the other hand suppresses SGs. This is consistent with the tumor suppressive role of senescence and the function of SGs as a cytoprotective mechanism that can promote tumorigenesis. It should be noted, however, that PAI-1 – a marker of senescence as well as a downstream effector and key component of SASP – is recruited to SGs (Omer et al. 2018). As translocation to SGs would prevent the secretion of PAI-1, SGs in this setting could, in theory, function to suppress SASP and the associated tumor-promoting activity. This raises a note of caution regarding SG inhibition for the treatment of cancer; while inhibition of SGs could push cells toward senescence and, thus, halt tumor growth, the lack of SGs in senescent cells could also aid tumorigenesis by contributing to SASP.

Several proteins and mRNAs that carry out cell division localize to SGs in cancer cells; this observation supports the idea that SGs play a role in coordinating cell proliferation. RBFOX2 is a member of the RBFOX family of proteins that regulate alternative pre-mRNA splicing and mRNA stability (Jin et al. 2003; Lovci et al. 2013). Under stress conditions, RBFOX2 is recruited to SGs via its RNA-binding domain and preferentially binds cell cycle-related mRNAs including retinoblastoma 1 (*RB1*) mRNA (Park et al. 2017). RB1 is a negative cell cycle regulator, and excess RB1 arrests cells in G1. This study proposed that SGs promote cell cycle progression via RBFOX2-mediated recruitment and inhibition

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of *RB1* mRNA translation (Choi et al. 2019). Recruitment of mRNA transcripts encoding for proteins involved in proliferation appears to be a general theme of SGs, as gene enrichment analysis of mRNAs in SG cores demonstrated that proto-oncogene transcripts (e.g., *ABL2*, *PDGFRA*, *GSK3B*, *RUNX1*, *AKAP11)* were highly enriched (Namkoong et al. 2018). Importantly, this study showed that while distinct stresses showed differences in the variety of mRNAs that were preferentially recruited to SGs, enrichment of proto-oncogene transcripts was shared across stress types. Given that proto-oncogene transcripts are rich in adenylate-uridylate (AU) sequences and consequently subject to mRNA processing and degradation, it has been suggested that recruitment to SGs may promote their stability, expression, and function to promote tumorigenesis (Namkoong et al. 2018). While several lines of evidence support a role for SGs in cancer cell proliferation under stress, studies also indicate that transcripts of both negative and positive regulators of proliferation are recruited to SGs. In addition, several of the protein components of SGs are involved in both negative and positive proliferation pathways. It is not clear how SGs would support cell proliferation by capturing proteins and mRNAs with seemingly opposite functions. It is possible that these components may be recruited at different levels relative to one another and that the sum of all parts ultimately favors proliferation.

In principle however, depending on cell intrinsic and extrinsic stimuli, the cellular levels of either positive or negative regulators of proliferation, as well as the levels at which they are recruited to SGs relative to one another, can shift. In addition, these transcripts could also be differentially modified through interactions with SG components with roles in mRNA processing and stability. As such, there is perhaps a context specific and dynamic balance between proliferative and anti-proliferative components of SGs. This would suggest that the impact of SGs on proliferation could also depend on context. With this in mind, it is interesting that primary osteosarcoma tumors where SGs were downregulated by shRNA-mediated knockdown of G3BP1 showed no difference in proliferation rate compared to control. Further studies are needed to understand whether this is specific to osteosarcoma or a shared phenotype of all tumors. However, this study may indicate that in the context of tumorigenesis, SGs may aid proliferation in later stages of tumor development or in specific cancer cell subclones, perhaps when a specific threshold of SG formation and SG signaling output is reached.

4.2 Stress Granules and Suppression of Cell Death

The relationship between stress granules and cell death is perhaps the earliest studied function of SGs. A number of in vitro studies demonstrate that SGs block the cellular apoptotic machinery that is triggered by stress stimuli in cancer cells, and several SG-mediated anti-apoptotic pathways have been defined. In addition, numerous studies have also shown that SGs are critical determinants of the sensitivity of cancer cells to chemotherapeutic agents.

4.2.1 Stress Granule-Mediated Suppression of Stress-Induced Apoptosis—

SGs control live-or-die cell fate decisions along two broad paths. The first is through the sequestration of pro-apoptotic factors, limiting their activity at their target locations. Secondly, SGs curb the production of reactive oxygen species, limiting apoptosis-inducing

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stress stimuli and cell damage. As discussed above, recruitment of components of the mTORC1 complex allows SGs to prevent mTORC1-hyperactivation-induced apoptosis in cancer cells. In addition, Arimoto et al. reported that SGs inhibit apoptosis by preventing p38 and JNK activation (Arimoto et al. 2008). Specifically, under oxidative stress conditions, SGs recruit RACK1 thus preventing its interaction with the MAPK kinase MTK1, which is required for p38/pJNK mediated apoptosis of cervical cancer cells (Arimoto et al. 2008). The coiled coil containing protein kinase (ROCK1) is another activator of JNK that is recruited to SGs (Tsai and Wei 2010). Sequestration of ROCK1 to SGs in cancer cells prevents the ROCK1-mediated phosphorylation of the JNK-interacting protein 3 (JIP)-3, thus inhibiting JNK activation and the induction of JNK-mediated apoptosis. In addition, translocation of TRAF2 to SGs inhibits TNF-mediated activation of nuclear factor (NF)-kB and apoptosis (Kim et al. 2005). Studies in non-cancerous cells show that SGs can recruit arginylated calreticutin to prevent its translocation to the plasma membrane and apoptotic function during stress; whether this mechanism also occurs in cancer cells remains to be determined (Lopez Sambrooks et al. 2012). More recently, it was demonstrated that macrophages utilize the SG translocation of DEAD-box helicase 3 X-linked (DDX3) to inhibit NLRP3 inflammasome activation (Samir et al. 2019). Activation of the NLRP3 inflammasome induces the secretion of pro-inflammatory cytokines and pyroptosis – a form of inflammatory cell death (Samir et al. 2019). Given the role of macrophages in driving tumor progression, it is tempting to speculate that SGs may promote tumorigenesis by preventing macrophage pyroptosis.

SGs have been shown to reduce ROS levels and ROS-dependent apoptosis; however, the mechanisms behind the antioxidant activity of SGs are not fully elucidated (Takahashi et al. 2013). One study identified an antioxidant function of the ubiquitin-specific peptidase 10 (USP10) and proposed that SGs may reduce ROS levels by facilitating the activation of USP10. It is currently unknown, however, how SGs may promote the antioxidant function of USP10 and how USP10 functions as an antioxidant (Takahashi et al. 2013). As discussed above, the NRF2 antioxidant pathway has been shown to promote SG formation. Given the role of SGs in regulating ROS levels, it would be interesting to determine whether SGs also impact the antioxidant activity of NRF2 (Mukhopadhyay et al. 2020).

4.2.2 Stress Granules and Chemotherapy Resistance—

Studies in various in vitro models have explored the relationship between SGs and cancer cell resistance to chemotherapy. These studies have shown that chemotherapeutic agents including bortezomib, cisplatin, etoposide, oxaliplatin, paclitaxel, and sorafenib induce SG formation. A comprehensive review of these studies has been recently published (Gao et al. 2019). This section highlights the most salient aspects of SG-mediated drug resistance.

A shared feature of all chemotherapeutic agents that drive SG formation is that they do so by inducing the phosphorylation of eIF2α. The exact kinases responsible for eIF2α phosphorylation, however, differ across agents. Sorafenib is a Raf1/Mek/Erk kinase inhibitor that is FDA approved for the treatment of patients with advanced hepatocarcinoma (HCC), renal carcinoma, and metastatic, progressive, and differentiated thyroid carcinoma refractory to iodine treatment. Sorafenib has been shown to induce SGs (Lin et al. 2012; Adjibade et al. 2015). Further studies showed that sorafenib treatment lead to the activation of the unfolded

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protein response (UPR) and induced SG formation via PERK-mediated phosphorylation of eIF2α (Adjibade et al. 2015; Pakos-Zebrucka et al. 2016; Feng et al. 2017).

Bortezomib is a proteasome inhibitor that is FDA approved for the treatment of multiple myeloma and mantle cell myeloma. Bortezomib treatment induced SGs in cancer cells of the colon, lung, cervix, head, and neck via HRI-mediated phosphorylation of eIF2α (Fournier et al. 2010; Kaehler et al. 2014; Burwick and Aktas 2017). Furthermore, bortezomib-induced SGs were shown to recruit and promote the degradation of transcripts of the cyclin-dependent kinase inhibitor p21 (WAF1/CIP1). As p21 is a protein that promotes cell cycle arrest and apoptosis, it was proposed that bortezomib-induced SGs lead to apoptosis inhibition and treatment resistance through downregulating p21.

Chemotherapeutic agents such as 5-fluorouracil (5-FU) cisplatin, etoposide, or oxaliplatin – which are used for the treatment of several cancers including colorectal, pancreas, breast, and head and neck – have been shown to induce SGs. 5-FU induces SG assembly by stimulating PKR-mediated phosphorylation of eIF2α (Kaehler et al. 2014). In all reported instances, SG formation in response to chemotherapeutic agents functioned as a mechanism of resistance to chemotherapy-induced cell death. In addition, inhibition of SGs, or of the kinases responsible for peIF2-α-mediated SG formation, sensitized cancer cells to chemotherapeutic agents.

Taken together these studies suggest that the blockage of SG formation would enhance chemotherapy cancer treatment. In addition, tumors driven by oncogenic pathways that stimulate SGs such as mutant RAS are well documented as refractory to chemotherapy. The capacity of these pathways to stimulate SGs therefore may also provide mechanistic insight into chemotherapy resistance and identify patients that could most benefit from anti-stress granule therapy.

4.3 Stress Granules and Tumor Metastasis

Invasion of local tissue and spread to distant sites to form metastases is a central feature of cancer and the primary cause of death for >90% of cancer patients (Hanahan and Weinberg 2011). Understanding the biological mechanisms of the metastatic process is crucial in finding successful therapeutic opportunities. The development of metastasis is a complex process that requires cancer cells to leave the local environment, circulate in the bloodstream, and acclimatize and survive the new environment of a secondary site. Consistent with the idea that highly metastatic cells utilize SGs for migration and survival, SGs have been observed in disseminated tumor cells isolated from the bone marrow specimens of breast cancer patients (Bartkowiak et al. 2015). In addition, Somasekharan et al. demonstrated that the metastatic potential of osteosarcoma cells is linked to SG formation (Somasekharan et al. 2015). SG inhibition by shRNA-mediated knockdown of G3BP1 led to an impairment of the invasive and metastatic potential of sarcoma cells in vivo. Formation of SGs in this study was linked to the upregulation of YB-1, which can directly bind to the 5’ UTR of G3BP1 mRNA to upregulate its translation. In agreement with these observations, a class I HDAC inhibitor suppressed sarcoma metastasis by enhancing YB-1 acetylation, which blocked the interaction of YB-1 with its mRNA target G3BP1, and downregulated G3BP1 levels and SG formation (El-Naggar et al. 2019). While the

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mechanisms through which SGs promote invasion and metastasis were unexplained in this study, the authors raised the possibility that SGs might sequester mRNAs encoding for proteins that inhibit invasion and metastasis. Sequestration of these mRNAs to SGs would prevent synthesis of the proteins they encode, thus enhancing the cellular capacity to invade and metastasize. In addition, based on the observation that G3BP1 knockdown reverted the growth pattern of primary tumors to noninvasive borders, this study proposed that SGs facilitate invasive capacity by selectively releasing mRNAs that encode matrix-degrading enzymes for translation.

Other studies suggest that SGs promote metastasis via inhibiting the ribonuclease inhibitor 1 (RNH1) which promotes metastasis through stimulating the activity of angiogenin (Pizzo et al. 2013). RNH1 is a component of SGs, and downregulation of RNH1 promoted migration and metastasis (Pizzo et al. 2013; Yao et al. 2013). Recruitment of RBFOX2 to SGs has also been shown to promote metastasis of melanoma cells to the lung as inhibiting the localization of RBFOX2 to SGs diminished lung metastasis in a mouse model (Choi et al. 2019). It is currently unknown how RBFOX2 recruitment to SGs may promote metastasis, but selective recruitment or exclusion of mRNAs encoding proteins, which inhibit or promote metastasis respectively, have been proposed as potential mechanisms (Choi et al. 2019). Another study in pancreatic cancer cells proposed that SGs may be implicated in the degradation of mRNA transcripts encoding for Binder of Arl Two (BART), which impairs cell invasion and metastasis by inhibiting ARL2-mediated activation of the RHO small GTPase, which is a key mediator of cell migration and metastasis (Taniuchi et al. 2011a, b). Although direct evidence that SGs contribute to *BART* downregulation is lacking, given that BART can be degraded by G3BP1, it is possible that SG formation enhances the interaction of *BART* mRNA with G3BP1 as well as *BART* degradation to facilitate cell invasion. Studies in noncancerous cells also showed that RHO is both a component and a mediator of SG formation, suggesting that a potential mechanism through which RHO promotes metastasis may be through SG formation (Tsai and Wei 2010). Taken together these studies indicate that while multiple lines of evidence point to a role of SGs in metastasis, further work is needed to identify and characterize the molecular mediators through which SGs may support this process.

5 Concluding Remarks

Stress adaptation, driven by dysregulated cancer signaling, is a fundamental property of cancer that has yet to be fully elucidated. As reviewed here, evidence from multiple in vitro and in vivo models indicates that oncogenic mutations and dysregulated signaling pathways in cancer modify the canonical molecules that regulate SG formation. By doing so, cancer cells take advantage of SG formation to enhance stress adaptation.

Oncogenic Ras mutations, hyperactivation of mTORC1 and HDAC, and dysregulation of glycolytic and hexosamine biosynthetic pathways have emerged as key pathways that stimulate SG formation in cancer cells. However, the full scope of oncogenic signaling pathways that may regulate SG formation remains to be established and may include a broader signaling network than is currently known. A recent study indicated that mutations in the E3 ubiquitin ligase binding adaptor SPOP1, which occur in ~15% of primary prostate

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cancers, led to enhanced SG formation in prostate cancer cells in vitro (Shi et al. 2019). As such, prostate cancers with SPOP1 mutations may be another example of tumors with enhanced SG formation and stress adaptation. Additional metabolic processes may also play an important role in SG formation in cancer. Glutamine deprivation was shown to impact SG formation in pancreatic cancer cells (Mukhopadhyay et al. 2020). However, cancer cells are depleted of several non-essential amino acids with roles in purine/pyrimidine synthesis, protein translation, and glutathione regulation which can impact translation inhibition and cellular stress and consequently SG formation. Lastly, protein levels of SG nucleators are upregulated in several tumors compared to normal tissue raising the possibility that higher levels of free SG-nucleator proteins in cancer may also amplify SG formation (French et al. 2002; Wang et al. 2018).

The initial view that SGs function solely to store RNA has been offset by a wealth of data that link SGs to several signal transduction and gene expression regulation pathways. In addition, it has been clearly demonstrated that the composition of SGs can vary significantly depending on the type of stress and tissue. The model that has emerged from these studies is that SG levels, composition, and dynamics determine their signaling output. As such, current studies aimed at understanding the role of SGs in cancer and their molecular mediators must address their context-dependent specificities and relevance.

Much remains to be learned about the cellular processes that SGs regulate in cancer and how they impact tumorigenesis. In addition, it still remains to be understood whether SGs are a feature of all tumors or only those of specific tissues (e.g., pancreatic cancer, osteosarcoma). As stress and the dysregulated signaling pathways described here are common in cancer, the expectation would be that SGs may also be a shared feature for most types of tumors. In the same vein, mTORC1, HDAC, and metabolic pathways are often dysregulated in the tumor stroma which is also exposed to stress stimuli. In addition, evidence that mutant KRAS can promote SG formation in a paracrine manner suggests that cancer cells may also instruct SG formation in the tumor stroma (Grabocka and Bar-Sagi 2016). The question that inevitably arises is whether SGs are present in the tumor stroma and does this impact tumorigenesis. It is also important to note that SGs are part of a larger group of stress-adaptive organelles that are hijacked by cancer cells under stress including macropinosomes, autophagosomes, and lysosomes (Commisso et al. 2013; Perera et al. 2015; Amaravadi et al. 2016). In yeast, SGs are cleared by autophagy, and evidence suggests that targeting of SGs to degradative organelles by autophagy may be conserved in mammalian cells (Buchan et al. 2013; Ryu et al. 2014; Marrone et al. 2018). This raises the possibility that SGs may interact and integrate with other stress-adaptive organelles in cancer. Such interactions could have important implications for the stress adaptation of cancer cells and tumor progression. Future studies aimed at answering these questions can provide important insight into the role of SGs in tumorigenesis.

Given the evidence that SGs may play an important role in tumorigenesis, it will be essential to develop animal models that assess their tumor-relevant functions. Development of tools for in vivo imaging of SGs in such models may allow visualization of the context-dependent specificities of their formation. Another current challenge is the lack of specific SG inhibitors. Current pharmacological agents that inhibit SGs have broad effects.

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Additionally, genetic inhibition of SG formation is usually achieved through targeting one or more SG nucleators which, generally, have functions beyond SGs. The understanding of specific interactions or modifications that determine the SG-nucleating capacity of these molecules is critical for the development of tools that allow for the distinction of their SG-specific function and roles in tumorigenesis. The exciting work that lies ahead to fully elucidate the function of SGs in tumorigenesis also has promising therapeutic prospects. Given the well-documented roles of SGs in the chemotherapeutic response, the development of anti-SG therapies has the potential to provide efficacious treatment modalities for cancer patients.

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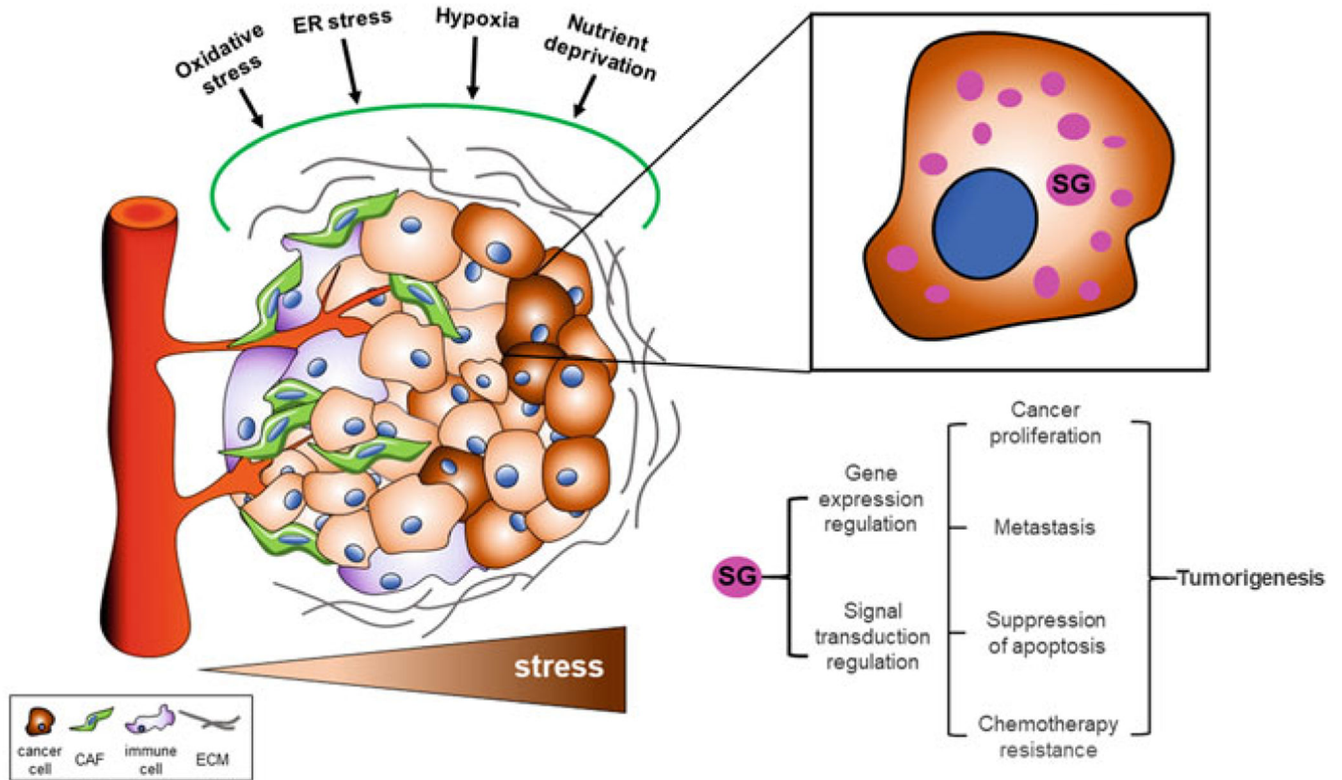

Fig. 1.

SGs are key regulators of tumor stress adaptation. Cancer cells are located in a complex microenvironment that is marked by high levels of stress stimuli (oxidative stress, ER stress, hypoxia, and nutrient deprivation). In order to survive under such adverse conditions, cancer cells must adapt. SG formation is one of the key strategies for cancer cells to adapt to the stress conditions. Recent evidence indicates that SGs may contribute to tumorigenesis by modifying gene expression and signal transduction programs that regulate cancer cell proliferation, invasion and metastasis, suppression of apoptosis, and chemotherapy resistance

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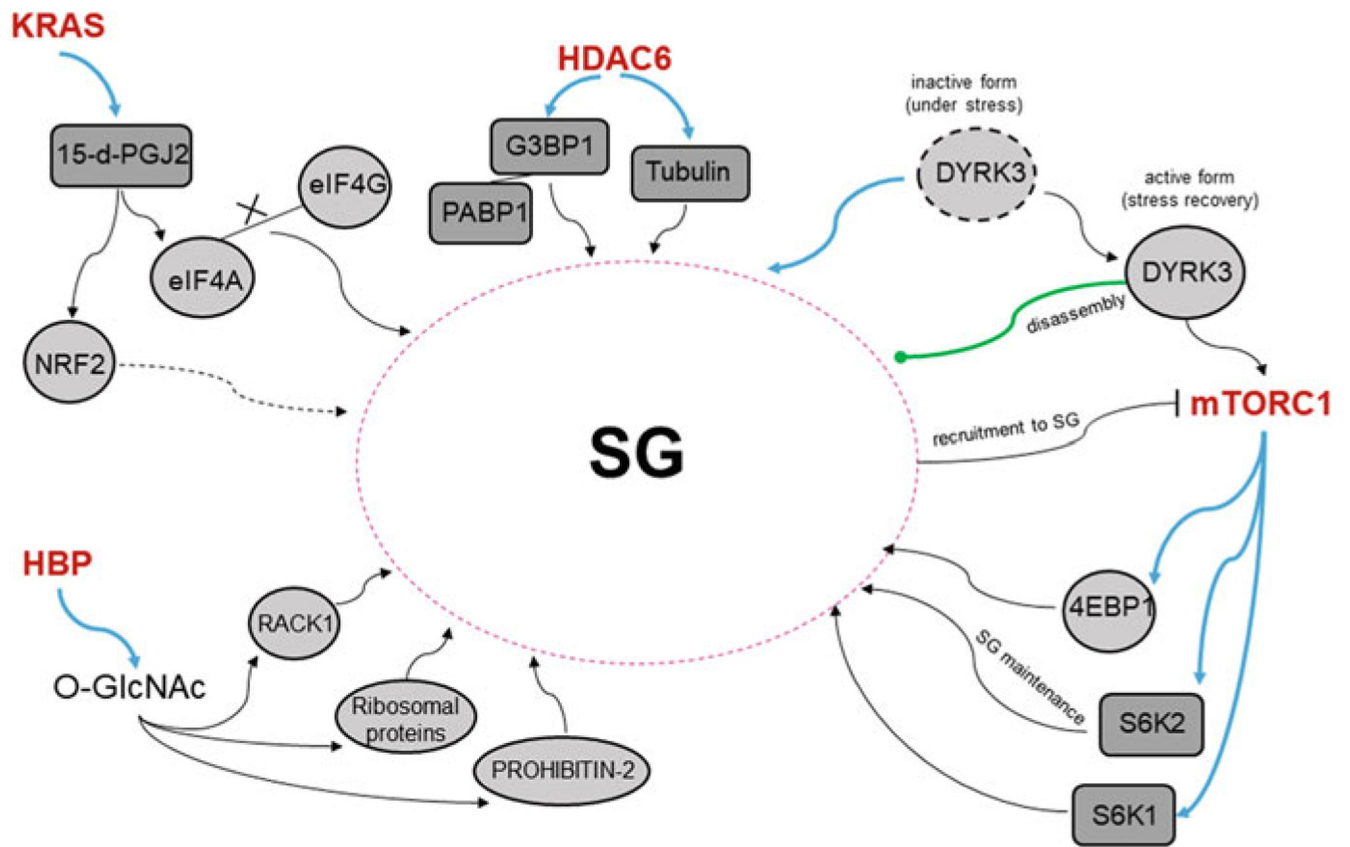

Fig. 2.

SG regulation by pro-tumorigenic signaling. Oncogenes (mutant KRAS) and activation of pro-tumorigenic pathways (mTORC1, HDAC6, HBP) promote SG formation through multiple molecular mediators. The SG regulators are involved in induction (blue arrows) or disassembly (green lines) of SGs