Apoptosis (2021) 26:371–384
https://doi.org/10.1007/s10495-021-01678-w

REVIEW

# Heat shock proteins-driven stress granule dynamics: yet another avenue for cell survival

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Accepted: 4 May 2021 / Published online: 12 May 2021


## Abstract

Heat shock proteins (HSPs) are evolutionary conserved 'stress-response' proteins that facilitate cell survival against various adverse conditions. HSP-mediated cytoprotection was hitherto reported to occur principally in two ways. Firstly, HSPs interact directly or indirectly with apoptosis signaling components and suppress apoptosis. Secondly, through chaperon activity, HSPs suppress proteotoxicity and maintain protein-homeostasis. Recent studies highlight the interaction of HSPs with cytoplasmic stress granules (SGs). SGs are conserved cytoplasmic mRNPs granules that aid in cell survival under stressful conditions. We primarily aim to describe the distinct cell survival strategy mediated by HSPs as the crucial regulators of SGs assembly and disassembly. Based on the growing evidence, HSPs and associated co-chaperones act as important determinants of SG assembly, composition and dissolution. Under cellular stress, as a 'stress-coping mechanism', the formation of SGs reprograms protein translation machinery and modulates signaling pathways indispensable for cell survival. Besides their role in suppressing apoptosis, HSPs also regulate protein-homeostasis by their chaperone activity as well as by their tight regulation of SG dynamics. The intricate molecular signaling in and around the nexus of HSPs-SGs and its importance in diseases has to be unearthed. These studies have significant implications in the management of chronic diseases such as cancer and neurodegenerative diseases where SGs possess pathological functions.

**Keywords** HSP · Stress granules · Cell-survival · Apoptosis · HSP70 · Chaperone

## Introduction

Cells are equipped with inherent self-protection systems in the face of various stress stimuli. Among the myriad of techniques used for self-protection, heat shock proteins (HSPs) comprise a major component that enables cells to avert damage and death in response to external stress. These multimolecular complexes comprise a major class of evolutionarily conserved proteins [1]. Studies of Ferruccio Ritossa in *Drosophila melanogaster* resulted in the discovery of these remarkable proteins in the early 1960s [2]. HSPs were initially found to be overexpressed in response to mild thermal stress. A multitude of cytotoxic stress conditions, such as oxidative stress, hypoxia, toxins, infections, and even inflammation was found to elicit HSP expression on later investigations. HSPs can hence be appropriately defined as stress proteins that facilitate cytoprotection under a wide variety of environmental, physiological and pathological adverse conditions.

HSPs work as a molecular chaperone to optimally fold nascent peptides and misfolded proteins, aid in the intracellular transport of proteins and also facilitate the degradation of misfolded proteins. They are markedly induced by several stimuli [3]. Cellular stress often results in failed assembly of protein complexes, protein misfolding, defective ribosomal products (DRiPs) due to incomplete translation and result in aggregation [4]. This induces the phosphorylation and trimerization of the HSP transcription factor, heat shock factor (HSF) in a Ras-dependent mode by MAPK kinases [5]. Hyper-phosphorylated HSF trimers transpose to the nucleus from the cytoplasm and induce gene transcription of HSP proteins [6].

SGs comprise another type of major cellular artillery which helps to cope up with various kinds of stress. Unlike

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HSPs, SGs are not studied extensively. They also possess a prominent role in triaging aberrant proteins into their core to avoid re-folding by HSPs [7]. *Prima facie* the actions of HSPs and SGs seem to be contrasting, yet both HSPs and SGs prevent apoptosis during cellular stress. Recent reports suggest the role of SGs in sequestering apoptotic proteins [8–10]. Considering, the central yet intricate role of these fascinating components in various pathophysiological conditions, further studies regarding their precise role in cellular homeostasis are indispensable before inducting HSPs as a potential drug target. In this review, we systematically analyzed the recent articles revealing the interactions of HSP superfamilies and SGs with cellular apoptotic machinery. We also discuss the association of HSPs with SGs in maintaining cellular homeostasis and survival.

## HSPs as master switches in balancing cell survival and apoptosis

### HSP superfamilies

HSPs are broadly classified into small HSPs (8–28 kDa) and large HSPs (40–105 kDa). However, HSPs are further grouped into superfamilies such as HSP100, 90, 70, 60, and the small HSP (sHSP), based on their molecular weight, structure as well as function [11]. Each of these families consists of many proteins that are expressed mostly constitutively and also inductively in response to cytotoxic stress. Among all these proteins, HSP27, HSP40, HSP70 and HSP90 as well as their transcriptional activator i.e. HSF1 are most explored hitherto in the context of apoptosis, SGs and cellular homeostasis.

HSPs contribute to cellular development, maintenance and survival by performing two major activities. Primarily, via their activities as molecular chaperons, it plays an important role in protein folding, transport and stabilization even in a normal cellular state [12]. It needs to be mentioned here that small HSPs act in an ATP-independent way whereas high molecular weight HSPs are ATP-dependent proteins [13]. Additionally, HSPs functions as a molecular inhibitor of apoptosis signaling cascades to sustain cell survival following exposure to damaging stimuli [13, 14]. Abnormal expression of HSPs is associated with the pathophysiology of several diseases such as neurodegenerative diseases, cardiovascular diseases and cancer. Our own and other research groups have reported elevated HSPs in several tumors, and in addition to the suppression of apoptosis, they substantially induce tumor progression and acquired drug resistance [15, 16]. HSPs are hence considered as potential diagnostic biomarkers and therapeutic targets in cancer management and treatment.

After cellular damage, two major cellular processes paradoxically get evoked, i.e., induction of 'stress response' and 'apoptotic cascade'. The interplay between these two processes determines the final cell fate to recover or die in response to cell injury. Stress inducible HSPs especially HSP27, 70 and 90 displays a pivotal role in modulating and shifting the axis of both the processes towards recovery and survival [17]. Studies so far have been suggesting two major roles of HSPs in cell survival, employing anti-apoptotic activity and its remarkable protein chaperone activity by which it refolds the death stimuli induced misfolded proteins, several of which are pro-apoptotic proteins [18, 19]. HSPs also forestall the accumulation of aberrantly aggregated proteins by the ubiquitin–proteasome system (UPS) or autophagy [20].

### Molecular basis of apoptosis

HSPs disable the engagement of apoptosis at several steps directly or indirectly to attribute cell protection and survival. Cellular apoptosis works either by way of 'intrinsic' (mitochondrial pathway) or 'extrinsic' (death-receptor pathway) signaling events. Both pathways activate a cascade of caspases (Cysteine-dependent aspartate specific proteases), a type of cysteine proteases that orchestrate the degrading of the cell [21]. Cascade of caspases comprises upstream *initiator* caspases for instances caspase 8, 9 and downstream *executioner* caspases such as caspase-3, 6 and 7. In both the apoptotic pathways (Fig. 1), assembling of adaptor molecules with initiator pro-caspases generate active forms of these proteases which cleave and activate the executioner pro-caspases [22].

(i) *Intrinsic pathway* It gets activated in response to intracellular stress generators such as UV, oxidative stress, etc. that activate pro-apoptotic proteins, Bax and Bak. Such proteins congregate on the mitochondria to prompt outer mitochondrial membrane permeabilization (MOMP). MOMP is synchronized by the dynamic interplay between the protein members of pro-apoptotic Bcl-2 family such as Bax, Bak, Bok and anti-apoptotic Bcl-2 family (Bcl-2, Bcl-xL, Mcl-1) as well as BH3 only protein family (PUMA, BIM, BID, BAD). BH3 only proteins assist in MOMP by impairing the activity of anti-apoptotic Bcl-2 proteins and thereby, activating pro-apoptotic Bcl-2 proteins [23, 24]. MOMP eventually leads to the release of several death molecules, for instance, cytochrome *c,* Apoptosis-inducing factor (AIF), Endonuclease G (Endo G), Smac, etc., resulting in caspase-dependent as well as independent apoptosis. Interaction of cytochrome *c* with procaspase-9 and cytosolic adaptor molecule apoptosis protease-activating fac-

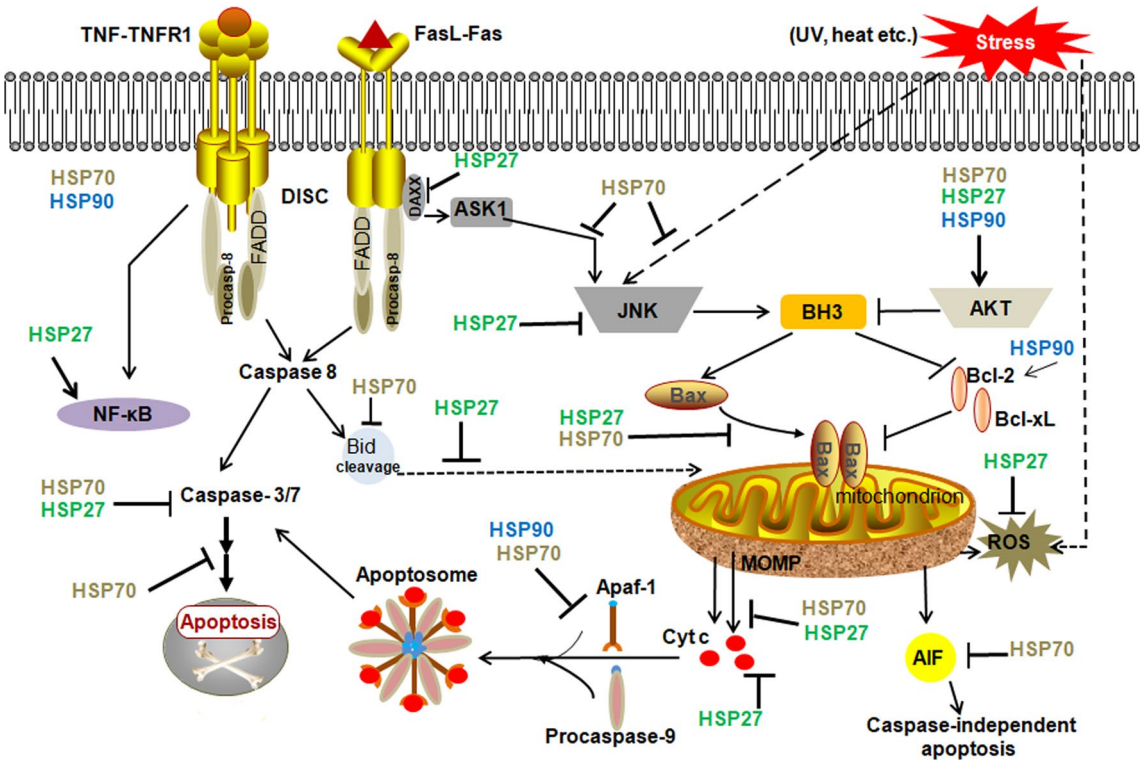


**Fig. 1** Schematic representation of HSP-mediated regulation of apoptotic pathways. Mitochondrial (intrinsic) pathway regulation by HSPs (i) upstream of mitochondria by modulating activation of stress kinases such as JNK, AKT, etc., inhibiting the activation of proapoptotic Bax, (ii) at mitochondrial level by inhibiting MOMP and release of death molecules such as cytochrome *c*, AIF, etc., and (iii) at post-mitochondrial level by blocking Apaf-1 mediated apoptosome formation, subsequent caspase-3 activation and downstream proteolytic signaling. HSPs also regulate Death-receptor (extrinsic) pathway by preventing the formation of Death Inducing signaling Complex (DISC) and therefore, inhibits procaspase-8 activation. Further, HSPs block caspase-8-mediated Bid cleavage and its translocation to mitochondria. Moreover, HSPs inhibit caspase-independent apoptosis by neutralizing AIF. HSPs also prevent DAXX-ASK1-JNK pathway

tor-1 (APAF-1) forms an 'apoptosome' complex which consecutively activates caspase-9 leading to caspase-3 activation [25, 26]. Smac/DIABLO and Omi/HtrA2 counteract the inhibitory effects of the inhibitor of apoptosis proteins (IAPs) and activate caspases. Similarly, upon release, AIF and Endo G translocate to the nucleus and mediate caspase-independent apoptosis by processing DNA cleavage and nuclear changes [27, 28].

(ii) *Extrinsic pathway* Here, the death signal is initiated due to the interaction of death receptors to their associated ligands such as Fas, tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL) resulting in the activation and trimerization of that specific receptor [29]. Activated receptor facilitates the recruitment of adaptor molecules such as Fas-associated protein with death domain (FADD) and consequently procaspase-8 recruitment at the cytoplasmic side [30]. This death-inducing signaling complex (DISC) mediates oligomerization and auto-activation of initiator caspase-8 which further activates downstream executioner procaspase-3 [24]. In parallel, activated caspase-8 can cleave Bid which can set off the mitochondrial pathway of apoptosis [31].

## HSPs: modulator of apoptotic signaling cascades

HSPs have key roles in modulating apoptosis by interacting with prominent proteins and enzymes in apoptotic machinery. For this reason, HSP regulation is now a thrust area for disease therapeutics. Here, we discuss the current knowledge accumulated so far with regards to different HSPs-mediated regulation of apoptosis.

*(i) HSP70:* HSP70 is a stress-induced protein encoded by closely related paralogs: HSPA1A and HSPA1B. Gene ablation studies by Schmitt et al. demonstrated a major chaperoning-dependent and independent anti-apoptotic role of HSP70 against a variety of lethal challenges [32]. HSP70 suppresses cellular apoptotic events directly and indirectly upstream and downstream of mitochondria [33]. Subsequently, it affects the MOMP, release of mitochondrial death factors, apoptosome formation and caspase activation. At a pre-mitochondrial stage, HSP70 bind and regulate

stabilization, cytoprotective or pro-apoptotic activities of several stress-induced kinases such as Akt, protein kinase c (PKC), JNK1, etc. [13]. HSP70 is also reported suppressing Bid mediated mitochondrial apoptosis by inhibiting MAP kinase JNK activity which indirectly, modulates the release of mitochondrial cytochrome *c* and SMAC [34, 35]. Pro-apoptotic Bax translocation on the mitochondrial membrane is hindered by the co-operative function of HSP70 and its DnaJ co-chaperones (dj1 and dj2) which consecutively reduces MOMP and release of cytochrome *c* and AIF [36]. The group led by Douglas Green reported that at the post-mitochondrial level, the ATPase domain of HSP70 directly interacts with Apaf-1 to inhibit the formation of apoptosome and subsequent caspase activation (Fig. 1) [37].

HSP70 suppresses the events downstream to caspase-3 activation in a TNFα- induced apoptosis even in the absence of the caspase-3 activity [38]. For instance, an interacting complex of HSP70 with co-chaperone HSP40 and inhibitor of caspase-activated DNase (ICAD) regulate the proper folding and enzymatic activity of caspase-activated DNase (CAD) resulting in DNA fragmentation and apoptosis [39]. Further, HSP70 is reported to bind with AIF directly and thereby, inhibits its nuclear translocation and subsequent chromatin condensation [40]. GRP78 (BiP), a vital HSP70 protein (HSPA5) in the endoplasmic reticulum (ER) is reported to suppress ER stress-triggered apoptosis [41]. Similarly, HSP70 maintains lysosomal membrane integrity under stress conditions to prevent the release of death molecules i.e. cathepsin proteases into the cell cytosol [42].

HSP72 (HSPA1A), the inducible form of HSP70, modulates the Fas ligand and TNF receptor (TNFR) mediated extrinsic pathway of apoptosis [43, 44]. Fas ligand-receptor interaction generally induces apoptosis through death-inducing signaling complex (DISC) assembly causing caspase-8 activation [45]. Alternatively, recruitment of adaptor molecule Daxx in DISC contributes to SAPK/JNK activation through apoptosis signal-regulating kinase 1 (ASK1) which leads to caspase-independent apoptosis [46]. HSP70 binds to Daxx and ASK1 and therefore, inhibits JNK mediated alternative route of apoptosis [47]. In contrast to the general assumption that HSP70 imparts protection against TNFR mediated apoptosis, researchers from the University of Cincinnati reported that HSP70 facilitates TNFR mediated apoptosis by interaction with IKKγ and inhibiting the activation of NF-κB signaling [48].

*(ii) HSP27:* HSP27 exhibits various major cellular functions including suppression of apoptosis, stabilization of cytoskeleton and reduction of proteotoxicity stress [49]. Oligomerized and phosphorylated HSP27 interacts with multiple proteins associated with apoptosis and significantly modulates apoptosis cascade at various stages. HSP27 regulates the activity of stress kinases JNK and AKT to promote cell survival (Fig. 1). Phosphorylated HSP27 binds to adaptor molecule Daxx resulting in the inhibition of ASK1 and JNK mediated apoptosis [50]. JNK protein, once phosphorylated, impairs the anti-apoptotic function of Bcl-2 and Bcl-xl. JNK also has the potential to enhance the mitochondrial translocation of pro-apoptotic Bax [51]. Studies by the group of Steven Borkan from Boston Medical Center also suggest that HSP27 prevents Bax activation via PI3-kinase-mediated Akt activation [52]. Multiple research groups have demonstrated the suppressor role of HSP27 in TRAIL and TNF induced apoptosis in various cell lines [53–55].

By interaction and stabilization of F-actin, HSP27 suppresses the translocation of Bid to mitochondria and subsequent MOMP [56]. At the post-mitochondrial stage, it reduces mitochondrial SMAC release [57]. HSP27 prevents engagement and activation of apoptosome by direct association with cytochrome *c* and APAF-1. Further, the interaction of HSP27 with procaspase-3 blocks caspase-9 mediated activation of caspase-3 [58].

*(iii) HSP90:* HSP90 is a highly abundant ATP-dependent molecular chaperone that regulates the balance of cell survival and death under the stress [59]. HSP90α and HSP90β are the most prominent isoforms of HSP90. HSP90α isoform gets expressed constitutively albeit in very less quantity but strongly induced by heat shock. Contrastingly, HSP90β gene is constitutively expressed at a notable level but weakly inducible by a heat shock [60].

HSP90 regulates several kinases and transcription factors that are crucial in apoptosis such as Akt, p53, NF-κB, etc. HSP90 stabilizes phosphorylated Akt which in-turn can phosphorylate and result in the inactivation of pro-apoptotic BAD and caspase-9 [61]. Akt driven phosphorylation degrades I-κB kinase and thereby promotes NF-κB mediated cell survival [62]. HSP90 also associate with mutated p53 and stabilize it and thereby block p53 mediated apoptosis [63].

In the TRAIL-induced death receptor pathway, HSP90α interacts and recruits anti-apoptotic FLIP(S) into the DISC complex upon binding of the TRAIL receptor to a ligand in glioma cells. FLIP prevents the recruitment and activation of procaspase-8 into DISC by interacting with the adaptor molecule FADD [64]. HSP90 is also reported to stabilize RIP-1 protein that upon recruitment to the TNF receptor-ligand complex promotes survival by the activation of NF-κB and JNK [65].

At the mitochondrial level, HSP90β is reported to prevent mitochondrial cytochrome *c* release by forming a complex with Bcl-2 in mast cells [66]. Interestingly, inhibition of mitochondrial-localized HSP90 *aka* TRAP-1 in tumor cells provokes MOMP and cytochrome *c* release [67]. Downstream of mitochondria, HSP90 directly associates with APAF-1 and blocks caspase-activation mediated by apoptosome formation (Fig. 1) [68]. Besides, it blocks caspases from getting activated by stabilizing IAP

family protein survivin [69]. In contrast, a few reports also suggested the pro-apoptotic effect of HSP90 based on the apoptotic stimulus and cell type. HSP90 implies its pro-apoptotic effect by regulating transcription factor HSF1 and other heat shock members. Depletion of HSP90 results in increased activity of HSF1 and elevated level of survival HSP70 protein [70].

Taken together HSPs have a very prominent regulatory role in suppressing extrinsic and intrinsic pathways of apoptosis (Fig. 1). In response to cellular stress, there will be an increased transcription of HSP genes. HSF-1 transcription factor presents in 'nuclear SGs' or HSF-1 granules perform this function and drive HSP expression and prevent apoptotic cascade [71]. Stress also induces the triage and deposition of survival and anti-apoptotic RNAs in cytoplasmic SGs. Studies from the last decade have found evidence on the interaction between HSPs and these cytoplasmic foci considering cell survival in the face of stress and injury.

## Stress granules: formation and role in cell survival

Eukaryotic cells are compartmentalized either as membrane-bound organelles or phase-separated non-membrane bound organelles, to limit their biochemical reactions in a specific locus. Various membrane-less organelles fall into the category of RNP granules and are formed due to the high concentration of RNA and proteins [72]. SGs are conserved mRNP granules present in cells to self-preserve under stressful conditions.

Cytoplasmic SGs are the reversible, dynamic cellular aggregates formed in the cytoplasm under various stress conditions such as nutrient starvation, oxidative, osmotic, toxin, or heat stress [73, 74]. Under cellular stress, protein translation gets impeded. SGs comprise untranslated mRNAs, translation initiation factors, various RNA binding and non-RNA binding proteins. It was widely accepted that SGs occur mainly due to translation initiation blocks. A highly comprehensive review of eukaryotic SGs-related studies by Ross Buchan and Roy Parker from the University of Arizona affirm that not all translation blocks result in the SG assembly [8]. This suggests that the formation of SGs occurs at some specific translation initiation steps under stress. SGs have two distinct layers: a core containing higher RNP concentration surrounded by a highly dynamic and less concentrated shell. The shell shares its components with other cellular compartments easily as compared to stable cores [73]. These two layers of SGs are currently assumed to have different components and dynamics.

### SG assembly and its constituents

SGs are dynamic as they assemble under stress and disassemble or get cleared by autophagy on alleviation of stress. Different types of interactions participate in SGs assembly. One such interaction is the protein–protein interaction that takes place between non-RNA binding proteins. Many protein modifications such as phosphorylation, acetylation, methylation and glycosylation revamp the protein–protein interactions, thereby affecting the SGs assembly [73]. Upon oxidative stress, eIF2α gets phosphorylated by certain kinases, thus halting the initiation of translation. This leads to the triage and accumulation of the translation initiation machinery proteins and RNAs into SGs [75]. Cumulating evidence suggests a model of 'liquid–liquid phase separation' (LLPS) in SG assembly. It is generally presumed that mRNPs first condense to become the core through strong and specific interactions. Later on, a high local concentration of intrinsically disordered regions (IDRs) of proteins on SG constituents would be inducing a LLPS, which is a promiscuous multivalent weak interaction resulting in the dynamic shell structure [73, 76].

Paul Anderson and Nancy Kedersha's seminal work described SG components which are broadly classified into specific groups [77]. The first class of SG components consists of the pre-initiation complex (PIC) comprised of halted initiation complexes that are bound to mRNAs, such as eIF3, eIF4F, eIF4B and 40S ribosomal subunit. EIF4A inactivation is involved in the SG assembly and mRNAs dependent on eIF4A based 5'UTR scanning are considered as prominent constituents for SG. The next class of SG components includes mRNA binding proteins especially translational inhibiting members and SG promoters such as cell internal antigen-1 (TIA-1) and TIA-1-related (TIAR), etc. The third type of SG proteins is RNA binding proteins that nucleate SG assembly, for instance, Ras GTPase-activating protein SH3-domain-binding protein (G3BP), caprin, etc. Though the composition of SGs varies under diverse stress conditions, yet only PICs and a limited number of RBPs are essential to guide SGs assembly, whereas other RNA binding proteins and non-RNA binding proteins, may serve the purpose of guiding mRNPs to the SGs.

Under heat shock, transcription of HSP mRNA as well as SG assembly occurs concurrently. Studies report that mRNAs encoding HSP70 and HSP90 are largely excluded from SGs and are retained in polysomes [78, 79]. It is presumed that the unique features of HSP70 mRNA are averting its recruitment into SGs. HSP70 mRNA are intronless ensuring rapid protein expression and may hence be less prone to SG formation. Kedersha and Anderson also reported that HSP70 mRNA has very long 5'UTR helping in its translation by avoiding eIF4A-based mRNA scanning [80].

### SG disassembly

Upon stress mitigation, normal SGs or rather reversible SGs start to get disassemble. The prominent cellular events in this cascade include eIF4E block removal, reactivation of eIF4A functions as well as translationally active PICs. Subsequently, the various mRNA bound proteins are displaced from SGs by ribosomes. In the following minutes, SGs shrink in size and finally disappear from the cytoplasm. SG-associated proteins such as USP10 along with HSPs contribute to the SG disassembly [81, 82]. The detailed mechanisms involved in SG assembly and disassembly are diagrammatically represented as Fig. 2.

## Autophagy-dependent/ independent SG clearance

In disease-linked aberrant SGs, disassembly is negatively affected resulting in the formation of irreversible SGs [83]. There occurs a transition from dynamic, reversible SGs toward aberrant SGs which are the hallmarks of several cancers. When cells are exposed to prolonged stress, reversible cytoplasmic SGs transform into irreversible SGs with more solid protein aggregates that do not contain high levels of mRNA [84]. RNA-binding proteins and SG core nucleating factors such as TIA-1, TIAR, G3BP1, etc. are aggregated in SGs [85, 86].

When the misfolded proteins exceed beyond the clearance capacity, a protein complex called 'aggresome' that sequester misfolded proteins is formed in cells. These aggresomes contain autophagic cargo such as HDAC6 [87]. Autophagic receptor, sequestosome-1 (p62) recognizes the Ubiquitin binding domain (UBD) of HDAC6 via linked ubiquitin and anchors the SGs to autophagy for clearance [88]. Autophagy-dependent SG disassembly occurs majorly by ULK1/2 mediated phosphorylation of VCP/p97 [89]. However, recent in vitro assays with autophagy or lysosome inhibitors such as ammonium chloride demonstrated that only a small fraction of SGs are disassembled by autophagy [90]. It is proposed that autophagy is not the favored mechanism for SG disassembly and that chaperone-assisted, autophagy-independent SG clearance is more prominent in cells.

The role of HSPs in regulating and preventing the formation of irreversible SGs by its action on intractable and abnormal protein aggregates is currently being studied. Strategies to reduce the number of SGs, especially those with aberrant misfolded proteins were proposed as a new way to target neurodegenerative diseases and cancers.

### Role of SGs in cell survival and diseases

Depending upon the stress conditions, the cells either activate their defense mechanisms or undergo death. SGs assembly is an adaptive defense mechanism of the cell that promotes cell survival by preventing the increased accumulation of misfolded proteins under type 1 stress conditions such as hypoxia, osmotic stress, etc. Arimoto et al. from The University of Tokyo reported that under type 2 stress situations as in exposure to radiation and toxins, stress-activated p38 and JNK MAPK (SAPK) signaling pathway are activated to induce apoptosis. Therefore, it was deduced that the proteins and kinases of the SAPK pathway get sequestered into SGs, and promotes cell survival by inhibiting apoptosis [9]. In line

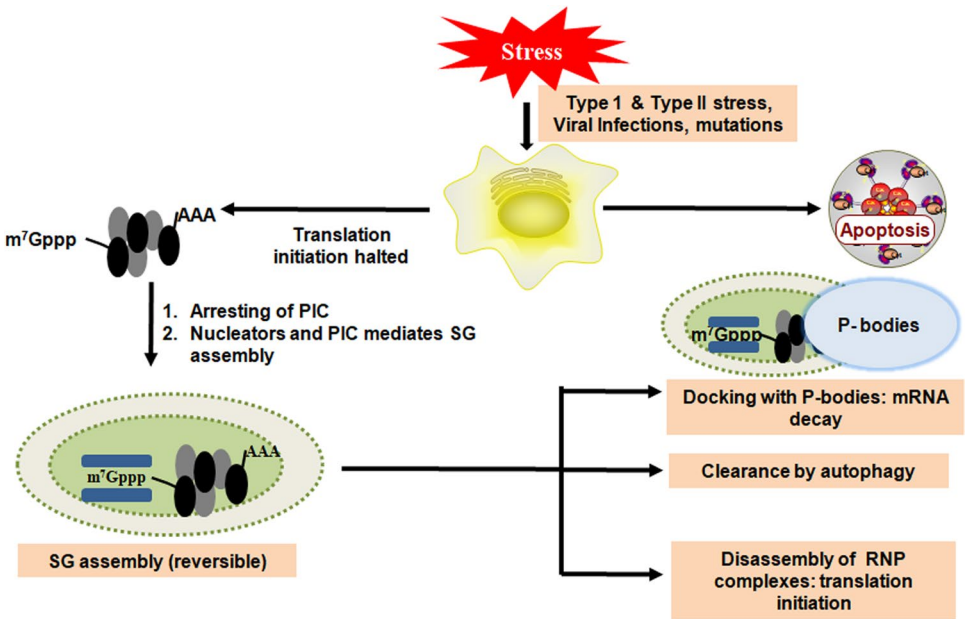


**Fig. 2** Formation and fates of SGs. Cells under stress may decide to undergo apoptosis or may activate the defense mechanism by sequestering translation initiation complex into cytoplasmic SGs and thereby, arresting translation of mRNAs localised in SGs. SGs are composed of untranslated mRNPs (mRNAs, pre- translation-initiating complex (PIC), ribonucleoproteins (RNP) and other signaling proteins. Upon the stress removal, SGs can either dock with P-bodies to degrade the mRNAs, translation of mRNA- protein complexes can be re-initiated or can be cleared via autophagy

with this observation, several other pieces of evidence highlighted the direct role of SGs in the inhibition of apoptosis. SG formation suppresses the production of ROS under stress conditions and hence inhibits ROS mediated apoptosis [91]. Cande et al. reported that the deletion of AIF either by knockout or RNA interference augments SG formation [92]. This remarkable study demonstrated a direct link between apoptotic molecules and SG assembly.

Under stress, cells suppress the translation of various proteins and promote SGs to prevent energy expenditure, while allowing selective protein synthesis essential for cell survival. SG assembling defects and stress sensing are prevalent in several devastating disorders. SG- mediated strategy of cell survival is exploited by cancer cells to survive under stress conditions. Recent evidence demonstrated the upregulation of several SGs components in various types of tumors [93]. This overexpression pattern significantly correlated with tumor pathogenesis, metastasis and also in chemoresistance. Tumor microniche is characterized by hypoxia, elevated ROS and insufficient nutrients. Consequently, as a stress response, SG assembly gets triggered in tumor cells. Several approved chemotherapeutic drugs and radiotherapy have been shown to induce SGs which may subsequently compromise the treatment efficacy and prognosis. In vitro inhibition of SGs formation sensitized cancer cells to undergo death by therapeutic drugs as observed by Timalsina et al. [94]. Interestingly, G3BP1 downregulation in a mouse model reduces SG assembly, precludes metastasis and controls tumor invasion [95]. These characteristics define SGs as a promising therapeutic target in cancer treatment.

Apart from the previously mentioned stresses, viral infections have also contributed to the formation of SGs. Infection with viruses such as dengue virus, reovirus, alphavirus, poliovirus and many more cause SGs assembly with a selective and unique composition [96]. These SGs do not get dissolved through the course of infection, hence serving as a mechanism for cell survival. Conversely, several proteins such as FUS and TDP-43 associated with the pathophysiology of various neurodegenerative disorders were found in SGs [97].

Altogether, SGs serves as the conserved strategy for the cell to survive under extreme stress conditions by arresting translation initiation complexes and performing as a signaling hub that can rewire signal transduction. It modulates proteostasis and ribostasis in cells to survive under unfavorable conditions [85].

## Heat shock proteins in stress granule assembly and dynamics

SGs were simply regarded as the hub for mRNA storage and processing until very recently. However, recent studies suggest that SGs also have an additional yet prominent role to protect the cell from unregulated aberrant protein aggregation [98]. HSPs have stellar properties as molecular chaperones to refold the misfolded proteins as well as nascent polypeptide folding. It is hence not surprising that HSPs and related chaperones work as crucial regulators of SG composition, dynamics and disaggregation. HSP chaperones constitute a protein quality control (PQC) system in cells and help in the dissolution of misfolded proteins and SG components in yeasts, drosophila and mammals [7].

As early as 1999, Kedersha et al. reported the heat shock-dependent aggregation of low molecular weight HSP27 (HSPB1) in SGs of human prostate DU145 cancer cells [99]. They also observed that HSP27 associates with SGs in response to only heat shock and but not against UV irradiation or chemical injury. This strongly suggests its specific role in SGs assembled due to temperature stimuli. Other SG components identified with HSP27 were TIA-1, TIAR, and PABP-I which are the core components of SGs and they aggregate irrespective of the kind of shock or injury. Following this finding, many canonical chaperones such as HSP22, HSP70 and HSP90 were associated with SGs in fungi and mammals by different groups of research teams globally [90, 100–102]. Due to the molecular chaperone activity, HSP's role in SG stability and disassembly is a thrust research area in drug design and therapeutics.

### HSP70 in SG dynamics and dissolution

Initial data on this line was on the HSP70 family, wherein the investigators reported that ATP driven HSP70 chaperone when overexpressed by induction or by transfection, restricts SG assembly [102, 103]. Later studies reported that HSP70 as well as HSP104 specifically facilitate the disassembly of SGs in yeast and mammals [104, 105]. Mateju et al. gave some enlightening information that HSP70s act to check the build-up of misfolded proteins in SGs [98]. Although it is well elucidated that HSP70 is required for efficient clearance of SGs after the removal of stress, the exact HSP70-SG dynamics is not yet known precisely. As mentioned earlier, the aggregation of TIA-1 or TIAR during SG assembly is regulated and blocked in the presence of high levels of HSP70 [102]. HSP70 favors the refolding of denatured cytoplasmic proteins when stress is induced. HSP70, for this reason, gets diverted away from TIA-1 due to its refolding function and hence free TIA-1 will aggregate which assists in SG nucleation. The proper renaturation of misfolded or denatured proteins releases HSP70 upon the alleviation of stress. Once free, HSP70 will target and solubilize TIA-1 and result in the clearance of SGs.

Interestingly, in contrast to the earlier concept that HSP inhibition is a causal factor in SG assembly, studies have shown that SG assembly precedes HSP70 inhibition. Hu et al. in their studies with YAMC colonic epithelial cells

demonstrated that under severe stress conditions, SGs recruit more HSP70 mRNAs into its core and thus reduce HSP translation and maintain its own integrity [106]. But under mild stress, higher levels of HSP70 mRNA obscure the inhibitory actions of SGs and help in HSP70 translation and which will, in turn, cause the disassembly of SGs on stress mitigation.

As it can be deduced generally, the HSP70 family may be working in parallel with other chaperones in SG clearance. The co-ordinated activity of HSP70 in SG clearance was reported in conjunction with HSP40 (Fig. 3). HSP40 proteins are demonstrated to enhance the ATPase activity of HSP70 proteins. HSP40 stimulates ATP hydrolysis by HSP70 and result in ADP bound high substrate-specific state of HSP70. Walters et al. in yeast have shown that different remodeling complexes of HSP40-HSP70 can lead to different fates of SG components and thereby determine the precise pathway for SG clearance [107]. Ydj1, a HSP40 family protein, co-ordinate with HSP70 assists in the disassembly of SGs and promotes protein translation. Sis1, which is another HSP40 protein, when acting in conjunction with HSP70 plays a role in triggering SGs to enter autophagy.

HSP70 has the unique ability to bind RNA and peptide targets independently. Peptide-binding functions of HSP70 are believed to cause their engagement in SG cores [108]. Although it is well known that HSP70 is essential for the well-organized disassembly process of SGs after stress removal, it is plausible that the RNA-binding ability of HSP70 might help in RNA triage roles of SGs too.

Recent evidence advocates a dual role of HSP70 in both assembly and disassembly of SGs in the context of cellular stress. HSP70 isoform (HSPA1A) engages with co-chaperones such as HSP22 (HSPB8) and BAG-3 (BCL2-associated athanogene) under stress conditions. This networking leads to SG assembly by inhibiting protein translation. As soon as the stress is relieved, HSP70 works towards the disassembly of SGs [90, 105]. Co-ordinated action of HSP70-HSP22-BAG3 was also found to suppress the deposit of defective ribosomal products, i.e., DRiPs in SGs. This complex based surveillance of SGs was termed as 'granulostasis' which is the maintenance of the integrity and dynamics of SGs by reducing chances of irreversible aggregation. Granulostasis occurs in two steps. Initially, HSP22 accumulates in SGs and prevents improperly folded proteins to form irreversible aggregates inside SGs. Later on, HSP22 recruits BAG3 and HSP70 to extract misfolded proteins to the perinuclear areas where they get targeted and labelled for autophagic degradation.

Considering the prominent role of HSP70 as an anti-apoptotic protein, it is more or less clear that low levels of HSP70 translation and subsequent high SG integrity is a plausible axis of apoptotic inhibition. This aspect as expected may have a negative influence on diseases like cancer and hence should work miraculously as a target for drug therapies. For instance, HSP70 binding co-chaperone HSP27/HSPBP1 is associated positively with SG formation and can inhibit HSP70 activity [109]. High HSPBP1 protein levels were observed by Raynes et al. in glioma, neuroblastoma tissues, as well as hepatocellular, prostate

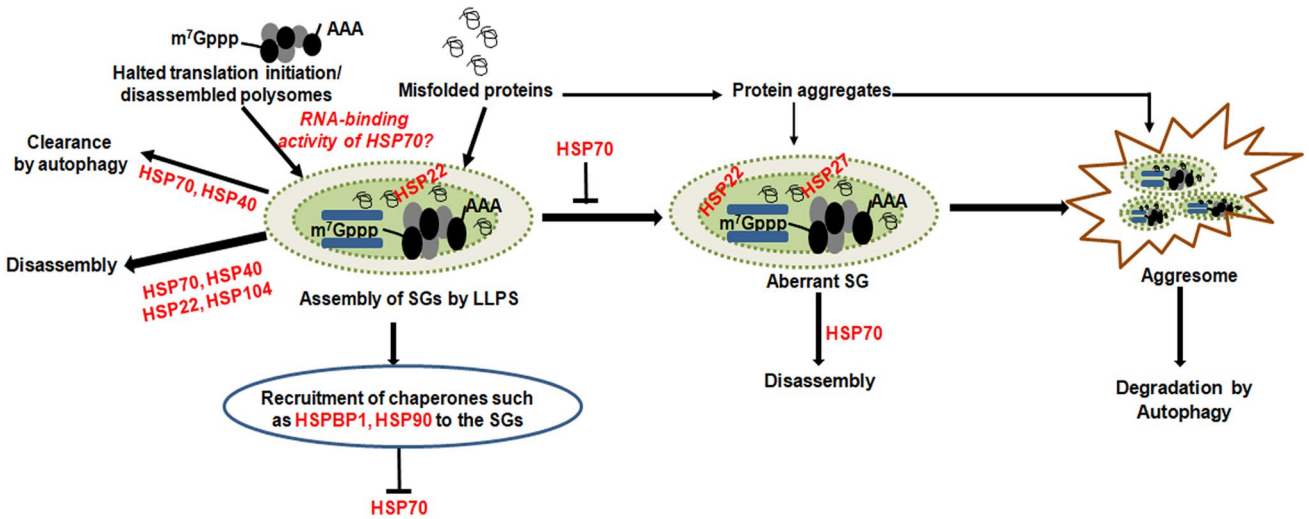


**Fig. 3** Model depicting the dynamics of SGs. Misfolded proteins can either form protein aggregates or may co-localize with the SGs. SGs mature by recruiting several other proteins including HSPs. Recruitment of HSPs such as HSP22 and HSP27 prevents aggregation of misfolded proteins in SGs which otherwise results in formation of an aggresome. HSP90 assists the recruitment of translation-initiation factor eIF4E and its binding partner into SG. HSP70 chaperone prevent the assembly and protein aggregation and thereby has a selective role in the disassembly of SGs. HSP70 in conjunction with other chaperons and co-chaperons, for instance HSP70-40 complex, determine the precise pathway for SG clearance

and lung carcinoma cell lines [110]. HSPBP1 interacts with the nucleators of SGs and poly-A mRNA and plays its role in forming SGs by phase separation [109]. Small molecular inhibitors of HSPBP1 may have a significant role in apoptosis induction in cancer cells. Targeting HSP70-SG dynamics through similar targets can make remarkable contributions to cancer therapy.

## HSP22/HSPB8 in SG dynamics

Small heat-shock proteins (sHSPs) were found to have a significant role in the assembly and disassembly of SGs. One major sHSP involved in SG function is HSP22 which in humans is encoded by the *HSPB8* gene. It is one of the HSPs which are immediately recruited into SGs upon stress (Fig. 3) [90]. During stress, HSP22 reduces the levels of aberrant proteins escaping degradation by promoting autophagic removal of misfolded proteins. It often functions as 'holdases' which are chaperones that bind misfolded proteins and confer to HSP70 for refolding or targeting them for degradation [111]. Ganassi et al. observed that inhibition of HSP70 caused high levels of HSP22 associated with DRiPs in SGs [90]. They inferred that HSP22 functions as a chaperone inside SGs and thereby stop the pathological irreversible aggregation of misfolded proteins. HSP22/HSPB8 expression is found to be induced by proteasome impairment but in normal unstressed cells, it is seen to be co-localized with DRiP-containing locations.

As detailed earlier, HSP22 with co-chaperones like BAG3 and HSP70 works as a PQC system to reduce the build-up of misfolding-prone proteins in SGs. Hence it ensures a dynamic state of SGs and their disassembly upon stress removal. When misfolded proteins such as DRiPs are trapped inside SGs, HSP22 is recruited first into SGs and it drives the BAG3-HSP70 complex to sort and process them by granulostasis. More studies are warranted to find the dynamic association between HSP22 and SGs so as to ascertain its role in adjunct therapies.

## HSP27/HSPB1 in SG dynamics

As mentioned earlier, the presence of the well-known sHSP, HSP27 (encoded by *HSPB1* gene) in SGs is well elucidated. sHSPs in SGs are regulated in response to stress conditions to facilitate cells to adapt and act in response to stress stimuli. When compared to HSP22, HSP27 is recruited at a later phase of SG assembly, when SGs have built up high levels of misfolded proteins (Fig. 3) [98]. Unlike HSP22, HSP27 is not considered critical in the assembly of SGs as the formation of SGs was not affected in the HSP27 knock out assays. Mateju and colleagues recently demonstrated that HSP27 is specifically recruited to SGs with misfolded proteins, indicating its role in SG disassembly and prevention from cytotoxicity. They further studied the temporal changes in SG formation in HeLa cell lines and found that HSP27 accumulated in SGs with time. This finding was corroborated by the observation that aberrant SGs containing DRiPs recruit HSP27 in addition to HSP22.

Most recent studies have elucidated the precise role of HSP27 in SG dynamics in the context of the SG component, FUS. FUS is a pro-survival nucleo-cytoplasmic shuttling protein that gets recruited to SGs during stress. RNA-binding proteins such as FUS contain prion-like domains undergo the LLPS process and result in amyloid aggregation in cells under stressful conditions [112]. Liu et al. proposed that HSP27 possesses a distinct role as the critical modulator of FUS in response to stress. HSP27 preserve FUS in a soluble state in normal cellular conditions [113]. Once cells are stressed, HSP27 gets phosphorylated. Meantime FUS relocates from nuclei to SGs. The phosphorylated HSP27 translocates into SGs and sustains the dynamic liquid-like state of FUS and prevents amyloid aggregation ensuring SG clearance which may happen after stress removal.

## HSP90 in SG formation

Similar to HSp70 chaperone, HSP90 mRNA transcripts were found to be actively excluded from sodium arsenite-induced SGs [79]. Suzuki et al. proposed that HSP90 chaperones play a role in the localization of eukaryotic translation initiation factor 4E (eIF4E) and associated eIF4E transporter (eIF4E-T) to SGs during assembly [114]. Moreover, HeLa cells when treated with HSP90 inhibitor Geldanamycin, SGs were affected in terms of size and localization. They also observed that important SG components eIF4E and eIF4E-T were lost from SGs in cells that were treated with HSP90 inhibitor. Matsumoto et al. took this study ahead by treating cells with Radicicol, another HSP90 inhibitor [115]. Similar to geldanamycin, radicicol also produced smaller and more dispersed SGs in the cytoplasm than those in untreated cells. These studies indicate the role of HSP90 in the SG assembly (Fig. 3) but not critical enough like other HSP chaperones. Further studies on this area are hence indispensable.

## Role of HSFs in SG dynamics

HSP expression is principally regulated by specific transcription factors called heat-shock factors (HSFs), which bind to the heat-shock promoter element (HSE). This family has four members (HSF1-HSF4) in vertebrates. HSF1 gets activated by high temperatures. HSF1 is organized into SGs during cellular stress. Phosphorylation and high transcriptional activity of HSF1 correlated with the presence of SGs [6]. Once stress is reduced, HSF1 dissociates from SGs and diffuses in the cell.

The Sistonen lab in Finland has made seminal discoveries in the field of HSFs. They found that HSF1 and HSF2 are novel stress-responsive constituents of the 'nuclear' SGs in human erythroleukemia and cervical cancer cells [116]. Based on the studies in deletion mutants, HSF2 promotes HSF1 localization in SGs [117]. Moreover, they indicate that HSF1 localization in SGs is strictly regulated by HSP70. Both gain and loss of DNA-binding activity of transcription factor HSF1 were demonstrated to correlate significantly with the assembly and disassembly of SGs, respectively [118].

An accumulation of persisting SGs seems to lie at the heart of several chronic diseases such as cancer as well as age-related neurodegenerative diseases. A more targeted and focused study on the involvement of HSPs in SGs will certainly allow faster progress in drug designing research. A schematic illustration portraying the dynamics of SGs in the context of HSP regulation is given in Fig. 3**.**

## Conclusions

HSPs are conserved molecular chaperones that are elevated in cells as a response against a wide variety of adverse stress. Apart from maintaining normal protein homeostasis through its chaperone activity, HSPs interact and suppress apoptosis signaling cascades under stress conditions. Recent studies have highlighted another promising cell survival strategy of HSPs as the regulator of SG assembly and disassembly. SGs are membrane-less, transient phase dense assembly under stress conditions constituted of mainly translation-stalled mRNAs, associated pre-initiation factors and specific RNA-binding proteins. As the prominent mRNA triage center in the cytosol, SGs enables the cell to reprogram its translational system for energy conservation. In addition, in a state of emergency, SGs function as the signaling hub to alter the multiple signaling pathways by intercepting and sequestering signal-transducing proteins. Hence, SGs promote cell survival by the maintenance of cytoprotective proteostasis and ribostasis, and by altering signaling. Notably, persisting SGs are emerging as the key player in the pathogenesis of diseases such as neurodegeneration, cancer, etc. establishing it as a potential therapeutic target domain.

Cumulating evidence indicates the prominent role of HSPs and related co-chaperones as the crucial regulators of SG composition, dynamics and disaggregation. For instance, HSPBP1 co-chaperone, HSP90 and HSP27 are shown to be recruited in SGs and mediate SGs assembly depending on the stress types. HSPBP1 interacts and inhibits the HSP70 activity of dissolving SGs. HSP90 and HSP27 interact with molecules of translation initiating complex which is recruited in SGs. Contrastingly, HSP70 interacts with other chaperones to form the HSPB8-BAG3-HSP70 complex, which mediates the role of PQC in dissolving SGs. HSP72 levels increase to disassemble the SGs, promote translation recovery, and also target proteins for degradation by inducing activation of UPS. Although these initial and preliminary studies have reflected an important association between HSPs and SGs, still extensive studies are warranted to explore this particular communion and its implications in diseases. Further studies in this direction are indispensable as HSP-SG axis will contribute tremendously to develop new and efficient therapeutic strategies for several diseases.

**Acknowledgements** MS acknowledges the financial support by SERB, New Delhi for the research project (CRG/2020/002009) that led to the conceptualization of the review. AV and MS thank the Head, Prof. Shyam S Chauhan and other faculties of Department of Biotechnology, AIIMS, New Delhi for their kind support. AV acknowledges Department of Biotechnology, Govt. of India for the fellowship. The authors sincerely acknowledge the research groups whose remarkable contributions brought us to the understanding of the emerging role of HSPs in SGs under stress conditions.

**Author contribution** MS conceived the overall theme and designed the review. MS, AV and SS performed literature search and prepared the manuscript. AV created the schematic diagrams. SS and MS critically reviewed and contributed to the final version of the manuscript. All authors read and approved the final manuscript.

**Funding** The current work was supported by the research grant from Science and Engineering Research Board (SERB), Department of Science and Technology, New Delhi, India (Ref. No. CRG/2020/002009) and AIIMS, Intramural Research Grant (A-830/2020/RS).

## Declarations

**Conflict of interest** All authors declare no potential conflicts of interest concerning the authorship and publication of this research article.

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