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Review

Mammalian RNA Granules

Aravinth kumar Jayabalan and Takbum Ohn†

Department of Cellular and Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Korea

RNA granules such as Stress Granules (SG) and P-Bodies (PB) are aggregates of translationally stalled messenger ribonucleoprotein (mRNP) complexes induced by a wide range of stresses. Over the past decade, extensive studies described key components of RNA granules, their molecular interactions and signaling pathways require for their assembly and disassembly. However, researches defining their exact roles under stress conditions have not been performed so far, although several studies suggested their roles in neurodegenerative diseases recently. In this review, we provide an introduction about their basic properties, key components, and the dynamic nature for their assembly.

Key Words: Stress granules, Translation initiation, eIF2α phosphorylation, RNA binding proteins

INTRODUCTION

In eukaryotes, translation can be divided into initiation, elongation, termination and ribosome recycling, in which translation initiation is considered as a highly regulated and sophisticated step as it allows rapid and reversible control of gene expression (Sonenberg and Hinnebusch, 2009). Translation initiation begins with the assembly of eIF2.GTP.Met-tRNAi ternary complex and, subsequent binding with the small (40S) ribosomal subunit to form 43S pre-initiation complex. The 43S pre-initiation complex is then recruited to the 5' end of mRNA containing various factors such as, eIF4F complex comprising cap binding protein (eIF4E), an RNA helicase (eIF4A) and a large scaffolding protein (eIF4G) and eIF3 and poly (A) binding protein (PABP). The pre-initiation complex then starts to scan in the 5' to 3' direction until it recognizes the initiation codon (AUG) which leads to codon-anticodon base pairing. After the recognition of initiation codon and 48S complex formation, eIF5 and eIF5B promote hydrolysis of eIF2-GTP and releases the Met-tRNA$_i$ into 40S subunit and facilitates joining of large (60S) ribosomal subunit to form 40S.Met.tRNA$_i$.mRNA complex to promote elongation (Jackson et al., 2010).

Gene expression change is the major consequence of stress responses along with alteration in cell metabolism, cell cycle progression, protein homeostasis, cytoskeletal organization and modification of enzymatic activities (de Nadal et al., 2011). Eukaryotic cells often change their gene expression profile according to the environmental for example, a number of adverse conditions such as heat shock, cold shock, hypothermia, oxidative stress, hypoxia, UV irradiation and viral infection admit the cells to reprogram or partially terminate their protein translation machinery in order to survive and overcome the damage caused by the unfavorable scenario (Holcik and Sonenberg, 2005). Many post-translational modifications allow the cell to adapt the stress rapidly such that it wouldn't spend much energy for the synthesis of unwanted protein and stored it for the repair of damage caused by the stress (Hilliker and Parker, 2008). Indeed, translation is selective under such conditions, translation of 25% mRNA's are selectively reduced whereas translation of 25% mRNA's (mostly transcripts encoding heat shock proteins) are significantly enhanced (Harding et

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†Corresponding author: Takbum Ohn. Department of Cellular and Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Korea.
Tel: +82-62-230-6285, Fax: +82-62-233-6337
e-mail: tohn@chosun.ac.kr

al., 2000a).

Stress induced translation arrest is predominantly the cause of eIF2α phosphorylation at serine 51 which converts eIF2 from a substrate to competitive inhibitor of eIF2B, thereby reduces the availability of eIF2.GTP.Met-tRNA$_i$ ternary complex required for translation initiation leads to global translation initiation shut down. This would cause the elongating ribosomes to run off their transcripts and form polyadenylated circularized mRNPs which acts as substrate for SG formation (Kedersha and Anderson, 2002). The adverse condition is sensed by a variety of eIF2α kinases, including **PKR** (Protein Kinase R), a double stranded RNA dependent kinase activated upon viral infection and cold shock (Srivastava et al., 1998; Hofmann et al., 2012); **PERK** (PKR like Endoplasmic Reticulum Kinase) is activated by endoplasmic reticulum (ER) stress when unfolded proteins accumulate in ER lumen (Harding et al., 2000b); **GCN2** (General Control Non-repressible 2) is activated in response to amino acid starvation and UV irradiation (Wek et al., 2006); **HRI** (Heme Regulated Inhibitor) primarily activated under heme deprivation and arsenite - induced oxidative stress and heat shock (McEwen et al., 2005). These kinases monitor different types of stress and regulate translation initiation through phosphorylation of eIF2α.

What are Stress Granules?

Stress granules are large, phase dense, non-membranous, microscopically visible aggregates of stalled translation initiation complex formed in the cytoplasm of stressed cells. Their size ranging from 0.1 to 2.0 μm depends on the type of stress and are usually appeared in stressed cells; in contrast, its closely related another RNA granule called PBs are present in unstressed cells and their number is increased upon exposure to stress (Anderson and Kedersha, 2009). Earlier, the function of SG assembly was implicated as cell survival mechanism but recent studies show that presence of SG is correlated with several diseases, neurodegenerative disorder (Ramaswami et al., 2013), resistance to radio- and chemotherapy (Fujimura et al., 2012), etc. Assembly of PB does not depend on SGs since P bodies are present in unstressed cells, but contradictory results were reported to explain whether SG assembly depends on PB? (Stoecklin and Kedersha, 2013). Some reports suggest SG formation depends on PBs (Kedersha et al., 2005) while other shows they are independent (Mollet et al., 2008). More than a decade, SGs formed by arsenite induced oxidative stress is considered to be 'canonical' or universal which are larger in size and mainly triggered by p-eIF2α until recently 'non-canonical' SGs were discovered. Non-canonical SGs are smaller and more numerous in number and are induced by the disruption of eIF4F complex (Richter and Sonenberg, 2005; Spriggs et al., 2010). Both canonical and non-canonical SGs differ by their mechanism of assembly, size and core components (Fujimura et al., 2012).

Components of SGs and PBs

The components recruited by stress granules and processing bodies exhibit discrete nature, SGs harbor translation initiation components whereas PBs mainly recruit enzymes involved in RNA decay machinery, yet both granules share some common proteins between them such as eIF4E and Rck.

The core components of stress granules include translation initiation factors such as eIF3, eIF4F complex (comprising eIF4E, eIF4A and eIF4G), small (40S) but not large (60S) ribosomal subunits, and cytoplasmic poly(A)-binding protein (PABP) (Kedersha and Anderson, 2007). Apart from translation initiation factors, SGs also recruit RNA-binding proteins such as TIA-1, TIAR, G3BP, FMRP, and FXR1 which are also required for SG aggregation (Kedersha et al., 1999), proteins involved in mRNA metabolism and signaling cascades such as TRAF2 and RACK1 (Kim et al., 2005; Arimoto et al., 2008). In situ hybridization studies showed poly $(A)^+$ RNA is also a component of SGs (Kedersha et al., 1999). In contrast to SGs, PBs mainly contains enzymes involved RNA degradation such as DCP1, DCP2, 5' to 3' exonuclease Xrn1, aggregation prone proteins such as Lsm 4, Edc3 and Pat1b and the scaffolding protein hedls/GE-1 (Stoecklin and Kedersha, 2013).

Some of the proteins shared between these two granules include cap binding protein (eIF4E), the RNA helicase

(RCK) and the argonaute proteins (Ago1 and Ago2). RNA binding proteins which maintain mRNA stability and translation such as poly (rC) binding protein (PCBP2), protein essential for embryonic development (Smaug), protein which controls mRNA polyadenylation (CPEB1), zinc finger protein (TTP) are also found to be present in both the granules (Kedersha and Anderson, 2007).

Recent evidence suggests that SGs sequester different types of components based on the type of stress they encounter. For instance, heat shock protein HSP27 is recruited to SGs under heat shock while it is selectively excluded in arsenite induced oxidative stress (Kedersha et al., 2005). RACK1, an apoptotic signaling protein is recruited under arsenite stress (Arimoto et al., 2008) but they are not observed in selenite induced oxidative stress (Fujimura et al., 2012). The functional significance for the localization of different components to SGs under various stress conditions is yet to be determined.

How SGs assemble and disassemble upon stress?

Cells sensitized to stress, they begin to slow down their activity by efficiently block protein synthesis and make the untranslated mRNAs locked inside the SGs so that they are readily available when the environment resumes to normal condition. Stalled translation initiation complex by eIF2α

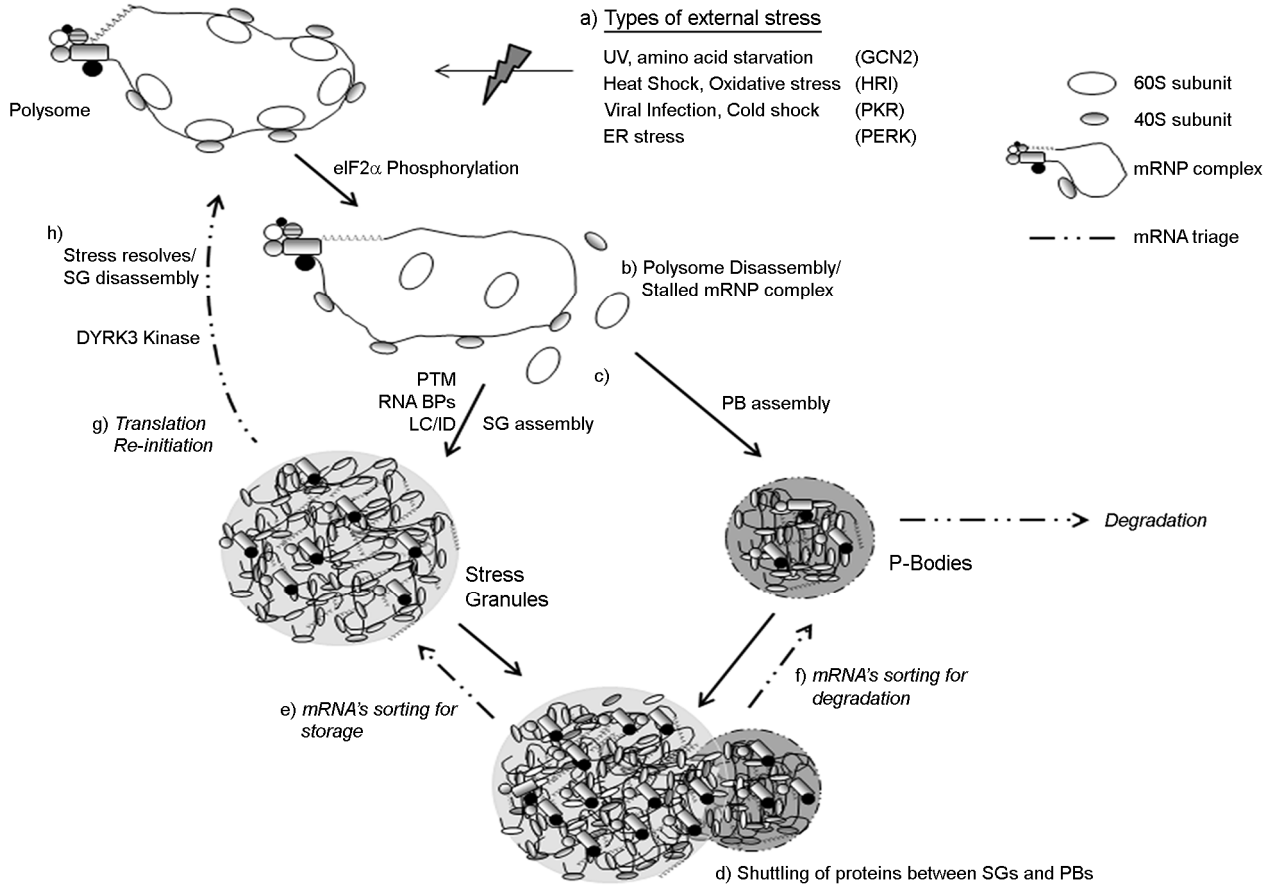

Fig. 1. Steps involved in SG assembly and disassembly: Mammalian cells often expose to **a)** various stress stimuli results in **b)** polysome disassembly by p-eIF2α, such disassembled mRNA's along with ribonucleoproteins (RNPs) aggregate together to form **c)** stress granules and processing bodies with the help of post-translational modifications (PTM), RNA binding proteins (RNA-BPs), high proportion of LC/ID region containing proteins, etc., with extended stress, they begin to **d)** dock each other to exhibit 'mRNA triage' by shuttling of proteins to determine the fate of individual mRNA transcripts., whether **e)** to store, **f)** to degrade or **g)** to reinitiate translation. When the stress is removed, **h)** SGs are disassembled with the help of DYRK3 kinase and the stored mRNAs begin to actively participate in translation.

phosphorylation reduces the availability of eIF2-GTP-tRNA ternary complex which serves as the signal for induction of stress granule formation (Fig. 1). The increased concentration of ternary complex gradually aggregates together with the help of numerous RNA binding proteins (TIA-1, TIAR, G3BP), proteins that have high level of low complexity region and several post-translational modifications (Kedersha et al., 2013). At first, SGs are smaller in structure and with increased exposure to stress; they slowly merge with neighboring granules and emerge into microscopically visible large structures. Although numbers of proteins are involved in SG assembly, TIA-1/TIAR, and G3BP are some of them whose role was deeply studied under real time.

TIA-1 and TIAR, members of RNA binding protein localized in nucleus, posses three RNA recognition motifs (RRM) at the amino termini and a glutamine rich prion related domain (PRD) at their carboxyl termini are extensively involved in RNA binding activity and self aggregation process respectively (Gilks et al., 2004). TIA-1ΔRRM truncation mutant which lacks RNA binding activity failed to assemble SGs in response to stress, suggests TIA-1ΔRRM acts as transdominant inhibitor of SG formation and functions downstream of eIF2α phosphorylation to sequester untranslated mRNAs to SGs (Kedersha et al., 1999). G3BP, an evolutionarily conserved RNA binding protein promote protein-protein interaction through its NTF2-like domain and RNA binding domain which contains RRM (RNA recognition motif) and arginine glycine box (Parker et al., 1996). Phosphorylation of G3BP at Ser 149 is critical for assembly of SGs; dephosphorylation of G3BP at Ser 149 promotes its ability to aggregate SGs, in contrast phosphorylated G3BP prevents its recruitment which is confirmed by mutant analysis where overexpression of non-phosphorylatable (S149A) mutant induces SG assembly but not phosphomimetic (S149E) mutant (Tourriere et al., 2003). Over-expression of G3BP itself can induce SG formation irrespective of any stress and the large G3BP induced SGs precedes eIF2α phosphorylation compared to small granules (Reineke et al., 2012). The current research on SG assembly involves the prediction of low complexity (LC) regions and intrinsically disordered (ID) proteins and their possible role in promotion of self aggregation (Kedersha et al., 2013).

A variety of post translational modifications also regulate SG assembly by interacting with different mRNP components directed to stress granules (Buchan and Parker, 2009; Ohn and Anderson, 2010). The primitive and most dominant modification of protein involved in SG assembly is phosphorylation of eIF2α which stalls translation initiation (Wek et al., 2006), whereas phosphorylation of TTP and G3BP selectively decreases SG assembly (Tourriere et al., 2003; Stoecklin et al., 2004). Other post-translational modifications such as O-GlcNAcylation of ribosomal proteins (Ohn et al., 2008), acetylation of HDAC6 (Kwon et al., 2007), methylation of FMRP (Dolzhanskaya et al., 2006), hypusination of eIF5A (Li et al., 2010) specifically regulate the assembly and disassembly of SGs.

The detailed mechanism of SG disassembly was not clearly known until a recent report identified DYRK3 (tyrosine-phosphorylation-regulated kinase 3) specifically regulates assembly and disassembly of SGs. When DYRK3 is active, it disassembles SG through its kinase domain and eventually releases mTORC1 and phosphorylates PRAS40, thereby allowing mTORC1 activation in unstressed cells. When DYRK3 is inactive, it assembles SG through its low complexity region at N-Terminal domain and sequesters mTORC1 in SGs (Wippich et al., 2013). During disassembly, the large granular structures begin to dissolve and disperse rather than fragment and are eventually cleared by autophagy and valosin containing protein (VCP). Inhibition of autophagy or depletion of VCP in cells affects the clearance of SG disassembly while recover from stress (Buchan et al., 2013).

Dynamic nature between polysomes, SGs and PBs

The close proximity observed between SGs and PBs exhibit 'mRNA triage', in which mRNAs destined for degradation are sorted to PBs, while transcripts necessary for translation reinitiation after stress recovery are stored in SGs (Anderson and Kedersha, 2008). The model for mRNAs in SGs and PBs are in dynamic equilibrium with polysomes revealed with the help of drugs that either freeze polysomes (cyclohexamide and emetine) prevent SG formation or

disassemble polysomes (puromycin) promotes SG assembly (Kedersha et al., 2005).

The dynamic nature at the molecular level was studied with the help of fluorescent tagged SG marker proteins in real time using time lapse microscopy. GFP-TIA1 is localized in nucleus as like endogenous TIA1 under normal condition. Under stress, GFP-TIA1 begins to accumulate evenly in cytoplasm in less than 5 minutes and with continued exposure of stress, they begin to fuse slowly and steadily and formed into few large discrete cytoplasmic foci. During recovery from stress, SGs disassemble with similar kinetics compared to assembly (Kedersha et al., 2000) but the kinetics is different with other types of stress; for example, cold shock induced SGs require hours to form and very few minutes to disassemble (Hofmann et al., 2012). One possibility for this phenomenon is the activation of different kinases which might follow different signaling pathways to assemble and disassemble SGs. Fluorescence recovery after photobleaching (FRAP) experiment identified the residence time of TIA-1 and PABP inside SGs. Under oxidative stress, GFP-TIA1 and GFP-PABP rapidly shuttles in and out of SGs. Interestingly 50% of GFP-TIA1 associated with SGs replaced every 2 seconds whereas 50% of GFP-PABP shuttles in and out every 20 seconds, the rate 10 times slower compared to GFP-TIA1. It shows TIA-1 is actively involved in escorting the untranslated mRNAs from polysomes to SGs which is central to the mRNA triage model (Kedersha et al., 2005).

CONCLUDING REMARKS

Stress granule assembly turn out to be an important phenomenon of eukaryotic cells under adverse environment to ensure that they can effectively overcome the unfavorable condition by reprogramming their translation apparatus such that it minimizes the stress induced damage to the cells (Sonenberg and Hinnebusch, 2009). Translation arrest provides a much needed break in translation rate; otherwise cells will actively engage in translating unwanted proteins. It is still not clear whether all the untranslated form of mRNAs are localized to stress granules. Even though the structure, composition and mechanism of assembly of SGs by arsenite induced oxidative stress was considered to be universal, recent reports suggest that even same kind of stress (eg., oxidative stress by sodium arsenite and hydrogen peroxide) assemble different form of SGs (with respect to structure and components) (Emara et al., 2012). The dynamic nature of SGs prevent the possibility of any biochemical purification for characterization at the molecular level, otherwise which could provide further insights about them.

One of the functions of stress granule is implicated as cell survival mechanism in which it recruits apoptotic signaling proteins (RACK1) under sub-lethal stress condition (Arimoto et al., 2008), although proper execution of apoptosis is required for cell differentiation and development (Riedl and Shi, 2004). Bortezomib, an anti-cancer drug induces stress granule whose effect is inversely correlated with cancer treatment and in rare cases, SGs increase resistance to chemo/radiotherapy (Fujimura et al., 2012). In addition, stress granules are involved in a variety of disease conditions such as cancer, fragile X syndrome, Ischemia reperfusion, spinal motor atropy, inflammatory disease (Calkhoven et al., 2002; Anderson and Kedersha, 2008). There is no wonder to observe distinct composition of SGs triggered by various types of stress but the unresolved question is how and why they sequester discrete components? Many answers will be uncovered if we reveal the significance of SG formation and its interaction with cellular pathways under stress and the signaling networks shared between them.

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