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Viral modulation of stress granules

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ABSTRACT

Following viral infection, the host responds by mounting a robust anti-viral response with the aim of creating an unfavorable environment for viral replication. As a countermeasure, viruses have elaborated mechanisms to subvert the host response in order to maintain viral protein synthesis and production. In the last decade, several reports have shown that viruses modulate the assembly of stress granules (SGs), which are translationally silent ribonucleoproteins (RNPs) and sites of RNA triage. This review discusses recent advances in our understanding of the interactions between viruses and the host response and how virus-induced modulations in SG abundance play fundamental roles in dictating the success of viral replication.

1. Introduction

Exposure of cells to environmental stress (e.g., heat shock, UV irradiation, hypoxia, endoplasmic reticulum (ER) stress and viral infection) trigger a rapid translational arrest generating polysome disassembly (Anderson and Kedersha, 2002). This event triggers a molecular triage, where the affected cell must make a decision on the fate of mRNA that is released from polysomes: decay or silencing (Anderson and Kedersha, 2008). For these events, cells have elaborated different classes of RNA granules named processing P-bodies (PBs) or stress granules (SGs) that contribute to the regulation and lifecycle of mRNAs. Both PBs and SGs contain share proteins and are assembled in cells subjected to stress, but differ in: (i) only PBs are observed in unstressed cells, (ii) SG assembly typically requires phosphorylation of translation initiation factor eIF2α, but not PB assembly (Fig. 1), and (iii) PBs contain proteins involved in mRNA decay, whereas SGs contain proteins of translation initiation complex (Eulalio et al., 2007).

PBs are cytoplasmic structures that, unlike SGs, are responsible for mRNA decay, RNA-mediated gene silencing (microRNA and siRNA-based gene silencing) and mRNA surveillance (or RNA quality control) (Beckham and Parker, 2008). PBs were discovered by Bashkirov et al. (1997) and they showed that XRN1, a 5′–3′ exoribonuclease, was localized in small granular structures within the cytoplasm. Other proteins related to mRNA degradation were also found to localize to this granules, such as a deadenylase (CCR4), decapping enzymes Dcp1 and Dcp2 as well as the activators of decapping Dhh1/p54/Rck/DDX6, Pat1, Scd6/RAP55, Edc3, Hedls and Lsm1–7 complex (Eulalio et al., 2007; Ingelfinger et al., 2002; van Dijk et al., 2002). Moreover, PBs can contain mRNAs and proteins involved in Nonsense-Mediated Decay (NMD) (e.g., SMG5, SMG7, and UPF1) (Fukuhara et al., 2005; Unterholzner and Izaurralde, 2004) and components of the *RNA-induced silencing complexes* (RISC) (e.g., argonaute, microRNA and GW182) (Liu et al., 2005; Rehwinkel et al., 2005) (Fig. 2).

On the other hand, SGs were first observed in the cytoplasm of plant cells exposed to heat shock (Nover et al., 1983). SGs are translationally silent ribonucleoproteins and serve as storage sites of mRNAs and proteins (Anderson and Kedersha, 2006) (Fig. 2), while other functions also have been discussed (Thomas et al., 2011). SGs typically contain poly(A)+mRNA, 40S ribosomal subunits, eIF4E, eIF4G, eIF4A, eIF4B, poly(A)-binding protein (PABP1), eIF3, eIF2, p54/Rck/DDX6, and many other RNA-binding proteins that regulate mRNA structure and function, including human antigen R (HuR), Staufen 1, polysomal ribonuclease 1 (PMR-1), Smaug, tristetraprolin (TTP), T-cell restricted intracellular antigen 1 (TIA-1) and TIA-1-related protein (TIAR), Fragile X Mental Retardation Protein (FXMR/FXR1), Ras-Gap SH3-binding protein (G3BP-1), cytoplasmic polyadenylation binding protein (CPEB) and Survival of Motor Neurons (SMN) protein, although the composition can vary (Anderson and Kedersha, 2006) (listed in Table 1).

During a stress response, cells induce a shut-off of cellular protein synthesis and subsequently promote SG assembly (Anderson and Kedersha, 2009). Different pathways in SG assembly have

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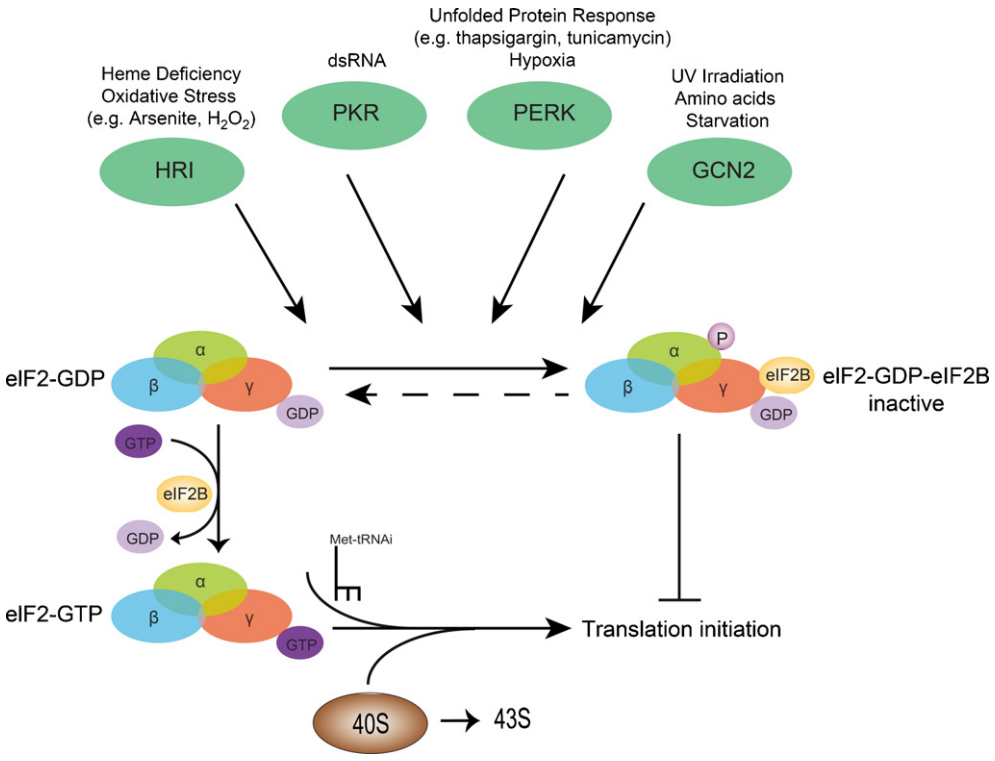

Fig. 1. Control of translation by eukaryotic initiation factor 2 (eIF2). eIF2 bound to GDP (eIF2-GDP) is recycled to the active eIF2-GTP by a reaction catalyzed by eIF2B. Once recycled, eIF2-GTP forms a ternary complex with initiator-methionine tRNA (Met-tRNAi) and 40S ribosome resulting in 43S pre-initiation complex. Four kinases activated by hemin deficiency/oxidative stress (HRI), viral infection (PKR), endoplasmic reticulum stress/hypoxia (PERK/PEK) and amino acid starvation/UV irradiation (GCN2); can phosphorylate eIF2 subunit α, stabilize eIF2-GDP–eIF2B complex (inactive) and prevents eIF2 recycling. These events result in a shut-off of the host protein synthesis and subsequently SG assembly (Fig. 2, i).

been described. The most popular pathway is the phosphorylation of the critical translation initiation factor, eIF2α by a family of four serine/threonine kinases HRI, PKR, PERK/PEK and GCN2. HRI (eIF2αK1) is activated in heme deprivation and oxidative stress (Han et al., 2001); PKR (eIF2αK2) is activated by viral infection (Williams, 2001); PERK/PEK (eIF2αK3) is activated in the presence of unfolded proteins in the endoplasmic reticulum (ER) and during hypoxia (Harding et al., 2000); and GCN2 (eIF2αK4) is activated during amino acid starvation and UV irradiation (Jiang and Wek, 2005). Each kinase causes the phosphorylation of the α-subunit of eIF2 at Ser52, which implies the tight binding with eIF2B, inhibiting the exchange of GDP for GTP (Fig. 1). Therefore, there is a decrease in translation tertiary complex assembly (eIF2/GTP/Met-tRNA) which suppresses the initiation of translation and promotes SG assembly (Fig. 2, step i) (Kedersha et al., 2002). Other mechanisms independent of the phosphorylation of eIF2α have also been explored. Hippuristanol and Pateamine A, drugs that inhibit the helicase activity of eIF4A, are able to induce the assembly of SGs (Fig. 2, step ii) (Dang et al., 2006; Mazroui et al., 2006). As well, the overexpression of SG markers (Anderson and Kedersha, 2008), such as TIA1 (Kedersha et al., 1999) or G3BP-1 (Tourriere et al., 2003), can trigger the assembly of SGs (Fig. 2, step iii).

The activation of eIF2α kinases by viral infection may result in the inhibition of cellular protein synthesis (Walsh and Mohr, 2011) and/or promotion of autophagy, process involving lysosomal-dependent recycling of intracellular components (Talloczy et al., 2002). Moreover, some viral proteins can bind eIF4A (Aoyagi et al., 2010; Page and Read, 2010). All of these mechanisms induce SG assembly (i.e., shut-off of cellular protein synthesis), but the viruses have found ways to bypass the hostile environment generated by the cell to ensure their survival. In the last decade, several studies have also demonstrated that the assembly of SGs can be dramatically influenced by viruses: the induction and blockage of SG assembly mediated by viral infections have both been described as means to promote virus replication (Beckham and Parker, 2008; Montero and Trujillo-Alonso, 2011; White and Lloyd, 2012). In this review we will summarize the current understanding that exists between different virus families and the regulation of stress granules.

Table 1
Stress granule components.

Protein	Reference
40S	Kedersha et al. (2002)
eIF2	Kedersha et al. (2002)
eIF3	Kedersha et al. (2002)
eIF4AI	Kedersha et al. (2002)
eIF4E	Kedersha et al. (2002)
eIF4G	Kedersha et al. (2002)
PABP-1	Kedersha et al. (1999)
p54/RCK/DDX6	Wilczynska et al. (2005)
TIA-1/TIAR	Gilks et al. (2004)
TTP	Stoecklin et al. (2004)
HuR/HuD	Kedersha et al. (1999)
Staufen 1	Thomas et al. (2009)
SMN	Hua and Zhou (2004)
G3BP-1	Tourriere et al. (2003)
Smaug	Baez and Boccaccio (2005)
FXMR/FXR1	Mazroui et al. (2006)
CPEB	Wilczynska et al. (2005)
PMR1	Yang et al. (2006)
RSK2	Eisinger-Mathason et al. (2008)
RACK1	Arimoto et al. (2008)
TRAF2	Kim et al. (2005)
FAST	Kedersha et al. (2005)
BRF1	Kedersha et al. (2005)