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Review

RNA granules: The good, the bad and the ugly

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ABSTRACT

Processing bodies (PBs) and Stress Granules (SGs) are the founding members of a new class of RNA granules, known as mRNA silencing *foci*, as they harbour transcripts circumstantially excluded from the translationally active pool. PBs and SGs are able to release mRNAs thus allowing their translation. PBs are constitutive, but respond to stimuli that affect mRNA translation and decay, whereas SGs are specifically induced upon cellular stress, which triggers a global translational silencing by several pathways, including phosphorylation of the key translation initiation factor eIF2alpha, and tRNA cleavage among others. PBs and SGs with different compositions may coexist in a single cell. These macromolecular aggregates are highly conserved through evolution, from unicellular organisms to vertebrate neurons. Their dynamics is regulated by several signaling pathways, and depends on microfilaments and microtubules, and the cognate molecular motors myosin, dynein, and kinesin. SGs share features with aggresomes and related aggregates of unfolded proteins frequently present in neurodegenerative diseases, and may play a role in the pathology. Virus infections may induce or impair SG formation. Besides being important for mRNA regulation upon stress, SGs modulate the signaling balancing apoptosis and cell survival. Finally, the formation of Nuclear Stress Bodies (nSBs), which share components with SGs, and the assembly of additional cytosolic aggregates containing RNA –the UV granules and the Ire1 *foci*–, all of them induced by specific cell damage factors, contribute to cell survival.

Contents

Abbreviations: ATXN2, Ataxin-2; BicD, Bicaudal D; CBP, CREB Binding Protein; CPEB, Cytoplasmic Polyadenylation Element Binding protein; DHC, Dynein Heavy Chain; DIC, Dynein Intermediate Chain; FAK, Focal Adhesion Kinase; FUS/TLS/hnRNP P2, Fused in Sarcoma; G3BP, Ras-GAP SH3 domain binding protein; GCN2, General Control Nonderepressible-2; Grb7, Growth factor receptor-bound protein 7; HAP, hnRNP A1 interacting protein; HDAC6, Histone Deacetylase 6; HRI, Heme-Regulated Inhibitor; HSF, Heat Shock Transcription Factor; KHC, Kinesin Heavy Chain; KLC, Kinesin Light Chain; MLN51, Metastatic Lymph Node 51; NMD, Nonsense mediated decay; nSBs, Nuclear Stress Bodies; OGFOD1, 2–14 Oxoglutarate and Fe(II)-Dependent Oxygenase Domain Containing 1; PB, Processing body; PERK, Pancreatic Endoplasmic Reticulum eIF2alpha Kinase; PKR/EIF2AK2, Double stranded RNA-dependent Protein Kinase; PP1, Protein phosphatase 1; PrP, Prion protein; RBP, RNA Binding Protein; RNP, Ribonucleoparticle; Sam68, Src associated in mitosis 68 kDa; Member of STAR, Signal Transducer and Activator of RNA; SCA, Spinocerebellar Ataxia; SG, Stress Granule; SMA, Spinal Muscular Atrophy; FMRP, Fragile X Mental Retardation Protein; SMN, Survival of Motor Neuron; TDP43, TAR DNA-binding Protein 43; TRAF2, TNF receptor associated factor 2; UVGs, UV RNA Granules.

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1. Introduction

The existence of cytoplasmic granules containing translationally repressed mRNAs in germ cells, embryos and neurons is known since a long time. These macromolecular aggregates are collectively called RNA granules, and the term defines a broad spectrum of entities, ranging from neuronal RNA transport granules to specific structures for the storage of maternal mRNAs. Two additional ubiquitous granules have been recently discovered, termed "Processing Bodies" (PBs) and "Stress Granules" (SGs). PBs were initially described as cytoplasmic aggregates harbouring the RNA decay machinery [1–4]. Then, work from several labs brought up the novel concept that PBs contain mRNAs that are silenced by a plethora of distinct mechanisms. Thus, cells show a variable number of PBs, depending on the amount of mRNAs under the control of silencing pathways including miRNA, RNAi, or NMD among others ([5–8] reviewed in [9–12]).

In addition to the numerous silencing pathways that operate in normal conditions, stress stimuli trigger several pathways leading to a global translational silencing, and this correlates with the formation of a distinct kind of mRNA silencing *foci*: the SGs. The formation of PBs and SGs has been recently discussed in a number of excellent reviews [9–11,13–15]. SGs and PBs are closely linked. SGs grow in close apposition with PBs and require their presence [16–18]. In addition, SGs and PBs share a few protein components, and mRNAs can be delivered from one structure to another (reviewed in [10–12,19]). A number of proteins stimulate the interaction between PBs and SGs, and a continuous spectrum of structures exists from PBs to SGs (reviewed in [10,20,21]). The cellular response to stress is highly conserved, and the formation of SGs was observed by us and other authors in trypanosomatid, yeast, mammalian, and insect cells ([10,17,18,22–38]. SG formation in procaryotes has not been reported, but chloroplasts –organelles of bacterial ancestry– assemble similar structures [36]. SGs have also been reported *in vivo*, indicating that SG formation is not restricted to the stress response of cells under in vitro conditions [39–41].

We and others have also documented the presence of SGs in myelinating and neuronal cells exposed to oxidative or ER-stress, or to pro-inflammatory cytokines, all conditions associated with neurodegenerative and demyeliniating pathologies (ref [16,39,40,42] and unpublished data).

The success of the stress response in helping cell survival depends on multiple mechanisms that act in concert to regulate cell metabolism, signaling pathways and gene expression at the level of transcription, translation and protein stability. Which is the relevance of SG formation to the survival response is a relevant question that we are beginning to understand, and that may have multiple answers.

2. PBs and SGs are related mRNA silencing *foci*

PBs are constitutive and can be further induced when a global translational silencing takes place, as it occurs upon a variety of stress insults, ranging from a raise in reactive oxygen species concentration to moderate hypoxia [6,17,20,43]. Whether PBs are a cause or consequence of mRNA silencing has been a matter of debate. Current evidence indicates that mRNA silencing by miRNA, RNAi or NMD (nonsense mediated decay) can occur in the absence of visible PBs [44]. However, oligomerization of PB components appears to be required for efficient silencing [45], and several proteins present in PBs contain specific aggregation domains, many of them being conserved among different species (Table 1) [18,46–53]. It is important to emphasize that the recruitment of mRNAs to PBs is not simply the consequence of not being translated, but rather the effect of an active silencing mechanism. An elegant study addressing this concept was performed by Izaurralde and co-workers, showing that the translational inhibitor puromycin –which interrupts translational elongation of all transcripts and thus flooding the cytoplasm with free mRNAs–induces PBs only in the presence of active RNAi or miRNA silencing pathways [44].

Numerous studies in yeast, plants, trypanosomatids, insects and vertebrates describe about half a hundred proteins present in PBs. These molecules include the 5′ cap binding protein 4E, decapping enzymes and co-activators, nucleases and several RNA-binding proteins involved in NMD, miRNA-mediated silencing and general mRNA repression (reviewed in [9–12]). In addition, a few splicing and mRNA export factors are also present. The presence of these factors in PBs has been studied mostly by imaging, and in most cases, they appear to display a quite uniform composition. However, many of these analyses include visualization of fluorescent chimerical proteins transiently expressed from transfected cDNAs. Extreme care should be taken when examining cells overexpressing PB components, as it was reported that alterations on the cellular stoichiometry may lead to aberrant structures, as a consequence of the intrinsic aggregative capacity of PB components, and of the titration of limiting factors [21,50,54]. Several reports where endogenous PB components were analyzed support the notion that heterogeneous populations of PBs are present. In mammalian cell lines, PCBP2, a facilitator of IRES-mediated translation, is present in a fraction of PBs identified by 4ET or DCP1a [55], and an important proportion of PBs lacks this protein. In the same line, a close examination of PBs in *Drosophila* Schneider cells reveals that Hedls, Dcp1a and XRN1 label distinct subsets of PBs, all of them being responsive to hypoxia (Fig. 1A, see also ref [43]). The heterogeneity is remarkable in mammalian neurons, where Cougot et al. have described specific *foci* termed dendritic P-body-like *foci* (dlPB). These contain the PB components DCP1a and GW182, whereas Ago2 and rck/p54 are not always present in dlPBs (Fig. 1B). Moreover, Ago2 and rck/p54 form *foci* that do not contain DCP1a nor GW182. In addition, unlike PBs in cell lines, dlPBs rarely contain XRN1 [56]. More recently, Bagni and collaborators reported the presence of an additional kind of dendritic *foci* that contain the PB component Lsm1 and exclude Dcp1a [57].

It is assumed that all these granules contain mRNA, but this has not been tested in all of them, and thus, the possibility that they represent storage sites for specific PB components remains open. Supporting this notion, satellite granules containing truncated Ge1/Hedls are detected adjacent to PBs [7,50]. Another structure associated to PBs and concentrating uridine-rich small nuclear ribonucleoproteins are the U bodies [58]. In this context, the heterogeneity of *foci* may be indicative of a maturation process where distinct factors are recruited progressively. PBs are motile, and they may come into close contact, and even fuse with each other [59–61], thus providing a way to exchange or incorporate distinct molecules. A model for PB assembly compatible with all of these observations was recently suggested [9]. According to this, silenced mRNPs are aggregated by specific dimerization or oligomerization domains (Table 1), which direct the