RNA granules

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Cytoplasmic RNA granules in germ cells (polar and germinal granules), somatic cells (stress granules and processing bodies), and neurons (neuronal granules) have emerged as important players in the posttranscriptional regulation of gene expression. RNA granules contain various ribosomal subunits, translation factors, decay enzymes, helicases, scaffold proteins, and RNA-binding proteins, and they control the localization, stability, and translation of their RNA cargo. We review the relationship between different classes of these granules and discuss how spatial organization regulates messenger RNA translation/decay.

Introduction

Nuclear mRNA transcripts acquire a protein coat composed of cap- and RNA-binding proteins that allow nuclear export and dictate the functional program of cytoplasmic mRNAs (Moore, 2005). Some mRNAs are programmed for immediate translation, a process that remodels the protein coat and assembles a polysome. After productive translation, mRNAs are deadenylated, polysomes are disassembled, and the mRNA is either degraded or stored. Other mRNAs are programmed for delayed translation, allowing transcripts to be transported or stored until developmental or environmental cues call for their translation. In both cases, a subset of translationally silenced mRNAs is packaged into RNP granules that lack a limiting membrane and are visible using light microscopy. Different classes of RNA granules share some protein components and may use similar mechanisms to regulate mRNA translation/decay.

Germ cell granules

Morphological descriptions of RNA granules originated with Metschnikoff (1865), who described dark staining granules at one pole within *Miastor metraloas* (fly) larvae. Subsequent studies showed that "polar granules" define sites of primordial germ cell differentiation in a variety of insect species (Ritter, 1890; Hegner, 1914). Analogous structures called germinal granules in *Xenopus laevis*, polar granules in *Drosophila melanogaster*, and P granules in *Caenorhabditis elegans* (here collectively referred to as germ cell granules [GCGs]) are RNP particles containing maternal mRNA that is required for germ cell specification (Schisa et al., 2001; Leatherman and Jongens, 2003). GCGs direct the timing of maternal mRNA translation to promote germ cell development in the early embryo and establish the germ line for the next generation. Germ cells contain other granules that may harbor translationally silenced mRNAs important for the development of other early embryonic tissues (Navarro and Blackwell, 2005). In addition to polyadenylated maternal transcripts (Schisa et al., 2001), GCGs contain proteins that regulate mRNA translation/decay, including the following: (1) multiple RNA-binding proteins, several of which are essential for both GCG structure and germ cell development (Fig. 1; Johnstone and Lasko, 2001); (2) CAR-1, an Sm protein related to Lsm proteins that regulate mRNA splicing, decapping, and decay; (3) CGH-1, an RNA helicase that is related to Dhh1 and p54/Rck, enzymes involved in translational silencing and decapping; (4) DCP1, a decapping enzyme; and (5) orthologues of the translation initiation factors eIF4E and eIF5A. Thus, GCGs contain proteins involved in translation initiation, translation control, and mRNA decay, which is consistent with their proposed role in the regulation ofs maternal mRNA expression.

Stress granules

Discovery. Many years after the description of GCGs, another RNA granule was observed in the cytoplasm of tomato cells subjected to heat shock. So-called heat stress granules (SGs) contain mRNAs encoding most cellular proteins but exclude mRNAs encoding heat shock proteins (Nover et al., 1989). Compositionally similar SGs appear in the cytoplasm of mammalian cells exposed to environmental stress (e.g., heat, oxidative conditions, UV irradiation, and hypoxia). In response to stress, eukaryotic cells reprogram mRNA metabolism to repair stress-induced damage and adapt to changed conditions. During this process, the translation of mRNAs encoding "housekeeping" proteins is aborted, whereas the translation of mRNAs encoding molecular chaperones and enzymes involved in damage repair is enhanced. Selective recruitment of specific mRNA transcripts into SGs is thought to regulate their stability and translation (Anderson and Kedersha, 2002).

Composition and internal dynamics. Stalled 48S preinitiation complexes are the core constituents of SGs, which include small but not large ribosomal subunits as well as

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Abbreviations used in this paper: GCG, germ cell granule; miRNA, microRNA; PB, processing body; SG, stress granule.

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Protein class	Protein component	Stress granule	Neuronal granule	Processing body	Germ cell granule
Ribosomes	40S	Kedersha et al., 2002	Krichevsky and Kosik, 2001	Unpublished data	ND
	60S	Kedersha et al., 2002	Krichevsky and Kosik, 2001	Unpublished data	ND
Translation	eIF2	Kedersha et al., 2002	Krichevsky and Kosik, 2001	Unpublished data	ND
	eIF3	Kedersha et al., 2002	ND	Kedersha et al., 2005	ND
	eIF4E	Kedersha et al., 2002	Smart et al., 2003	Kedersha et all, 2005	Amiri et al., 2001
	4E-T	ND	ND	Ferraiuolo et al., 2005	ND
	PABP	Kedersha et al., 1999	Krichevsky and Kosik, 2001	Kedersha et al., 2005	ND
	RCK/CGH-1	Wilczynska et al., 2005	ND	Cougot et al., 2004	Navarro and Blackwell, 2005
	TIA-1/R	Kedersha et al., 1999	ND	Kedersha et al., 2005*	ND
RNA stability	TTP	Stoecklin et al., 2004	ND	Stoecklin et al., 2004	ND
	HuR/D	Gallouzi et al., 2000	Atlas et al., 2004	Unpublished data*	ND
RNA-binding proteins	Staufen	Thomas et al., 2005	Thomas et al., 2005	Unpublished data	ND
	SMN	Hua and Zhou, 2004	ND	ND	ND
	G3BP	Tourriere et al., 2003	Atlas et al., 2004	Kedersha et al., 2005	ND
Sm/Lsm proteins		Unpublished data	ND	Ingelfinger et al., 2002; van Dijk et al., 2002	Audhya et al., 2005; Boag et al., 2005
Decapping	DCP1/2	Kedersha et al., 2005	ND	Ingelfinger et al., 2002	Lall et al., 2005
Exonucleases	XRN1	Kedersha et al., 2005	ND	Bashkirov et al., 1997	ND
siRNA	GW182	Kedersha et al., 2005	ND	Eystathioy et al., 2003	ND
	Argonautes	Unpublished data	ND	Liu et al., 2005b	ND

Figure 1. **Comparative composition of cytoplasmic RNA granules.** Green, present; red, absent. *, weakly present.

the early translation initiation factors eIF2, eIF3, eIF4E, and eIF4G (Kedersha et al., 2002; Kimball et al., 2003). In addition, SGs contain PABP1 (Kedersha et al., 1999), the p54/Rck helicase (Wilczynska et al., 2005), the 5′–3′ exonuclease XRN1 (Kedersha et al., 2005), and many RNA-binding proteins that regulate mRNA structure and function, including HuR, Staufen, Smaug, TTP, Fragile X mental retardation protein, G3BP, CPEB, and SMN (see Fig. 1 for specific references). SGs also contain putative scaffold proteins such as Fas-activated serine/threonine phosphoprotein (Kedersha et al., 2005). Like tomato heat SGs, mammalian SGs selectively exclude mRNAs encoding stress-induced heat shock proteins (Kedersha and Anderson, 2002). However, SGs are not stable repositories of untranslated mRNA, as drugs that stabilize (e.g., cycloheximide) or destabilize (e.g., puromycin) polysomes inhibit or promote SG assembly, respectively, which is indicative of a dynamic equilibrium between these structures (Kedersha et al., 2000). Moreover, FRAP analysis reveals that many SG-associated RNA-binding proteins (e.g., TIA-1, TIAR, TTP, G3BP, and PABP) rapidly shuttle in and out of SGs despite the large size (several micrometers) and apparent solidity of these cytoplasmic domains (Kedersha et al., 2000, 2005). Given that these proteins also regulate mRNA translation and decay, their rapid flux through SGs supports the notion that SGs are triage centers that sort, remodel, and export specific mRNA transcripts for reinitiation, decay, or storage. At the same time, SGs contain components with no obvious link to RNA metabolism, notably TRAF2 (Kim et al., 2005), which is recruited to SGs via its binding to eIF4G and may link SGs to apoptosis.

Assembly and function. Unlike other RNA granules, SGs are not seen in cells growing under favorable conditions but are rapidly induced (15–30 min) in response to environmental stress. The phosphorylation of translation initiation factor eIF2α by a family of stress-activated kinases (e.g., protein kinase R [PKR], PKR-like ER kinase, GCN2, and heme-regulated inhibitor) is critical for the assembly of SGs. Phosphorylation of eIF2α reduces the availability of the eIF2–GTP–$tRNA_i^{Met}$ ternary complex, thereby blocking translation initiation and promoting polysome disassembly. The following data establish the central importance of phospho-eIF2α in SG assembly: (1) the expression of a recombinant phosphomimetic mutant of eIF2α (S51D) is sufficient to induce the assembly of SGs (Kedersha et al., 1999); (2) the expression of a recombinant nonphosphorylatable mutant of eIF2α (S51A) prevents the assembly of SGs (Kedersha et al., 1999); and (3) mutant mouse embryonic fibroblasts expressing only the nonphosphorylatable form of eIF2α (S51A) do not assemble SGs in response to heat, arsenite-induced oxidative stress, or FCCP-induced metabolic stress, but they can assemble SGs when transfected with recombinant eIF2α (S51D; McEwen et al., 2005). Thus, phospho-eIF2α is essential for SG assembly.

Several proteins act downstream of phospho-eIF2α to potentiate or inhibit SG assembly. Self-aggregation of either TIA proteins or G3BP promotes SG assembly. Stress-induced aggregation of TIA proteins is mediated by a glutamine-rich prionlike domain that is regulated by HSP70 (Gilks et al., 2004). Similarly, self-aggregation of the RNA-binding protein G3BP (Ras-GAP-SH3–binding protein) promotes SG assembly, a process that is regulated by phosphorylation at serine 149 (Tourriere et al., 2001). Although not present in SGs, the mitochondria-associated apoptosis-inducing factor inhibits SG assembly by shifting the cellular redox potential (Cande et al., 2004). Finally, various mitochondrial poisons induce SGs, suggesting a requirement for ATP in either SG assembly or disassembly

(Kedersha et al., 2000, 2005). Thus, SG assembly/disassembly is regulated by numerous signaling pathways acting downstream of phospho-eIF2α.

SGs are also detectable in tissues from stressed animals. In chickens treated with the ototoxic antibiotic gentamycin, the appearance of SGs in cochlear cells (Mangiardi et al., 2004) occurs several hours before the onset of apoptosis. In another study, whole-animal radiotherapy induces SG assembly within individual tumor cells (Moeller et al., 2004), in which the radiation-induced translation of hypoxia inducible factor–1α-regulated transcripts is delayed pending SG disassembly during recovery, suggesting that the expression of these transcripts is inhibited by their retention in SGs. Similar results have been described using an animal model of stroke, in which SGs may regulate protein translation in neurons during ischemia (Kayali et al., 2005). These studies indicate that SGs are not in vitro artifacts of cell culture but are an integral part of the organism response to stress.

Processing bodies

Discovery. The processing body (PB) is a distinct cytoplasmic RNA granule that contains components of the 5′–3′ mRNA decay machinery, the nonsense-mediated decay pathway, and the RNA-induced silencing complex. The focal distribution of mammalian 5′–3′ exonuclease XRN1 (Bashkirov et al., 1997) provided the first intimation of the spatial regulation of mRNA decay (Bashkirov et al., 1997). Subsequent studies demonstrating the focal distribution of other RNA decay factors such as the decapping enzymes DCP1/DCP2 and the Lsm proteins (Bashkirov et al., 1997; Eystathioy et al., 2002, 2003; Ingelfinger et al., 2002; van Dijk et al., 2002, 2003) supported a model of spatially discrete mRNA decay foci. Functional studies in yeast confirmed this model by demonstrating that mRNAs containing 5′–3′ exonuclease-resistant oligo-G tracts accumulate at these foci, leading to their designation as PBs (Sheth and Parker, 2003). Similarly, knockdown of XRN1 leads to the accumulation of poly(A)$^+$ mRNA at PBs in mammalian cells (Cougot et al., 2004). Whereas SGs are heterogeneous in size and shape, PBs are uniform spheroid particles that increase in size and number in response to stress (Kedersha et al., 2005; Teixeira et al., 2005; Wilczynska et al., 2005).

Composition. The components of PBs have been defined in complementary studies in lower and higher eukaryotic cells (Bashkirov et al., 1997; Eystathioy et al., 2002, 2003; Ingelfinger et al., 2002; van Dijk et al., 2002, 2003). PBs contain enzymes that are required for each phase of the general mRNA decay pathway, including a deadenylase (CCR4), a decapping enzyme complex (including DCP1/2, Hedls, hEdc3, and p54/RCK; Fenger-Gron et al., 2005; Yu et al., 2005), and an exonuclease (XRN1). PBs also contain an Lsm1–7 heptamer that regulates various aspects of RNP assembly (Ingelfinger et al., 2002) and components of the nonsense-mediated decay pathway (e.g., SMG5, SMG7, and UPF1; Unterholzner and Izaurralde, 2004; Fukuhara et al., 2005). In mammalian cells, PBs contain components of the RNA-induced silencing complex (e.g., argonaute and microRNA [miRNA]; Liu et al., 2005b; Sen and Blau, 2005), the eIF4E-binding protein 4-ET, and GW182, an RNA-binding protein required for miRNA-dependent silencing (Jakymiw et al., 2005; Liu et al., 2005a; Rehwinkel et al., 2005). The translation initiation factor eIF4E and the translational silencer/RNA helicase p54/RCK are also found in PBs, suggesting that they are sites of translational control as well as mRNA decay. Finally, PBs contain several RNA-binding proteins associated with mRNA translation/decay, including TTP, BRF1, CPEB, 4-ET, and Smaug (Fig. 1).

Function. Many important functional studies of PBs were performed in *Saccharomyces cerevisiae*, which lack SGs (Teixeira et al., 2005). Yeast PBs exhibit many properties common to mammalian SGs: (1) both increase in size and number in response to glucose deprivation, osmotic stress, and UV irradiation (Teixeira et al., 2005); (2) both contain mRNA in equilibrium with polysomes (Brengues et al., 2005); and (3) Dhh1p/Pat1p-enforced polysome disassembly causes PB assembly in yeast (Coller and Parker, 2005), whereas puromycin-enforced polysome disassembly causes SG assembly in mammalian cells (Kedersha et al., 2000). Studies in fission yeast indicate that *Schizosaccharomyces pombe* assembles SG-like structures containing eIF3, eIF4A, and RNA in response to heat shock (Dunand-Sauthier et al., 2002), making speculation as to the possible evolutionary relationship between SGs and PBs premature. In mammalian cells, SG formation requires eIF2α phosphorylation, whereas stress-induced PB formation does not (Kedersha et al., 2005). The signaling pathways that regulate PB assembly remain to be determined. Recent work in mammalian cells defines a PB core complex (Fenger-Gron et al., 2005), which is likely to be a key player in PB assembly.

Many metazoan PB components (hedls, GW182, and eIF4-ET) have no yeast counterparts, yet knocking down any one of these inhibits PB assembly and impairs PB function. For example, knockdown of 4E-T or GW182 concurrently inhibits adenine/uridine-rich element–mediated (Ferraiuolo et al., 2005; Stoecklin et al., 2006) and short inhibitory RNA–mediated (Jakymiw et al., 2005; Liu et al., 2005a; Rehwinkel et al., 2005) mRNA decay. Mammalian PBs are sites of miRNA-mediated translational silencing (which has not been reported to occur in yeast). Reporter transcripts targeted by miRNAs accumulate at PBs in a miRNA-dependent manner (Liu et al., 2005b; Pillai et al., 2005), and mutations that displace argonaute from PBs abrogate the translational silencing of its target reporter mRNAs (Liu et al., 2005a). Collectively, these results indicate that PBs house multiple mRNA decay and silencing processes.

Although PBs and SGs are distinct structures, they share many components (Fig. 1) and interact with one another in stressed mammalian cells. Real-time fluorescence imaging shows that PBs are highly motile, whereas SGs are relatively fixed, although SGs exhibit fission, fusion, and occasional dispersal, which is consistent with their proposed role in sorting and export of their contents (Kedersha et al., 2005). When a motile PB encounters an SG, it is immobilized in an apparent "docking" process. After spending some minutes tethered to the SG, it can disengage and resume its cytosolic survey. As destabilizing factors such as TTP and BRF1 promote interactions

between SGs and PBs, mRNAs marked by these proteins may be delivered from SGs to PBs for decay. Thus, SGs act as intermediates between polysomes and PBs and may sort and modulate the increased flow of untranslated mRNA that accompanies stress. The close relationship between SGs and PBs in mammalian cells reiterates the dynamic link between mRNA translation and mRNA decay in yeast (Coller and Parker, 2005).

Neuronal granules

Neurons have evolved unique mechanisms that enable events initiated at the cell body to rapidly trigger protein synthesis at distant synaptic surfaces. This entails packaging mRNA into neuronal granules for transport to sites of translation. Neuronal granules harbor translationally silenced mRNAs that are transported to dendritic synapses, where they are released and translated in response to specific exogenous stimuli (Krichevsky and Kosik, 2001; for review see Kosik and Krichevsky, 2002). They contain mRNA, small and large ribosomal subunits, translation initiation factors (e.g., eIF4E and eIF2α), and RNA-binding proteins that regulate mRNA function (e.g., HuD, G3BP, Sam68, SYNCRIP, hnRNP A2, RNG105, FMRP, and Staufen; see Fig. 1 for references). Despite the presence of intact ribosomes, mRNA associated with neuronal granules is not translated until it arrives at the synapse, where its translation may require an activating stimulus. For example, in neuroblastoma cells, zipcode binding protein 1 (ZBP1) facilitates the transport of β-actin mRNA along neurites. During cytoplasmic transport, ZBP1 inhibits the translation of its associated transcripts. When β-actin transcripts reach the periphery of the cell, the Src-dependent phosphorylation of ZBP1 releases the mRNA and allows the synthesis of β-actin protein (Huttelmaier et al., 2005). SGs and neuronal granules share many protein components (Fig. 1), and Staufen can be transferred from neuronal granules to SGs in response to stress (Thomas et al., 2005). These results reveal a dynamic interrelationship between various types of RNA granules.

Links between RNA granules

All RNA granules harbor translationally silenced mRNA. GCGs and neuronal granules harbor highly specific mRNA cargo, whereas SGs and PBs are less discriminating. SGs contain the majority of polyadenylated mRNAs that are subject to stress-induced translational arrest but exclude mRNAs encoding stress-induced proteins such as HSP70. PBs contain mRNAs subject to general, nonsense-, and adenine/uridine-rich element–mediated decay as well as mRNAs targeted by miRNAs and short inhibitory RNAs. Fig. 1 lists representative proteins from different functional classes that are components of RNA granules. Although the content of each type of RNA granule is distinct, many proteins are found in more than one type of granule. Besides varying in mRNA selectivity, different RNA granules contain or exclude ribosomes. Neuronal granules appear to contain both large and small ribosomal subunits, which are packaged in an inert fashion that prevents translation. SGs contain only small ribosomal subunits derived from disassembled polysomes, whose mRNA is being remodeled and sorted for export to other sites. Finally, PBs lack ribosomal subunits altogether, nor do they contain translational initiation factors (other than eIF4E). Thus, the ribosomal composition of these granules correlates with their functions: neuronal granules house pretranslational mRNA, SGs harbor mRNA from translationally terminating RNA (e.g., disassembling polysomes), and PBs contain mRNA selected for decay.

Despite recent progress, we know almost nothing about the signaling pathways and molecular mechanisms governing formation and disassembly of mRNA granules. We lack a complete list of components for a single type of RNA granule, even within a single species or cell type. In all likelihood, yeast genetics will continue to point the way toward understanding PB dynamics and regulation, but because many relevant PB components (e.g., GW182, hedls, and argonaute) are not found in yeast, studies of higher eukaryotes are also essential. A deeper understanding of the smallest and most ancient RNA granule may reveal principles that are applicable to the other granules described in this study. To borrow on an analogy, mRNA molecules lead complicated lives (Moore, 2005) and complicated deaths. Each mRNA transcript exhibits changes in wardrobe and location that correlate with its functional state throughout its lifetime. Protein coats are added cotranscriptionally and are then modified during splicing and transport to the cytoplasm. Cytoplasmic transcripts may be bundled into a germ cell or neuronal granule for maturation or transport to the worksite, dressed in a different protein uniform, and released for productive translation. If the cellular economy sours (stress), the transcript may be temporarily retired to an SG. If the cellular economy recovers, the transcript can redress and resume production at a polysome. If the cellular economy remains depressed, the transcript can be delivered to a PB to die. Thus, the localization of the transcript is linked to changes in wardrobe (protein clothing) and functional state (translating, silenced, or decaying). Whether the protein coat determines or reflects the localization and functional state of a mRNA transcript appears to be a "chicken or egg" question at present. Nevertheless, our understanding of the complicated lives of mRNA requires further elucidation of the key molecular events that dictate its wardrobe, location, and functional state.

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