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mRNP granules
Assembly, function, and connections with disease

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Abbreviations: mRNP, messenger ribonucleoprotein; IMC, inter-mitochondrial cement; HSP, heat shock protein; 4E-BP, eIF4E binding protein; RISC, RNA induced silencing complex; FRAP, fluorescence recovery after photobleaching; MSP, multi-system proteinopathy; ALS, amyotropic lateral sclerosis; FTLD, frontotemporal lobar degeneration.

Messenger ribonucleoprotein (mRNP) granules are dynamic, self-assembling structures that harbor non-translating mRNAs bound by various proteins that regulate mRNA translation, localization, and turnover. Their importance in gene expression regulation is far reaching, ranging from precise spatial-temporal control of mRNAs that drive developmental programs in oocytes and embryos, to similarly exquisite control of mRNAs in neurons that underpin synaptic plasticity, and thus, memory formation. Analysis of mRNP granules in their various contexts has revealed common themes of assembly, disassembly, and modes of mRNA regulation, yet new studies continue to reveal unexpected and important findings, such as links between aberrant mRNP granule assembly and neurodegenerative disease. Continued study of these enigmatic structures thus promises fascinating new insights into cellular function, and may also suggest novel therapeutic strategies in various disease states.

Introduction

mRNA regulation is a crucial means by which cells control gene expression, as it enables both rapid and local changes in synthesis of specific proteins to occur. Three key aspects of mRNA regulation include control of mRNA localization, mRNA translation, and mRNA stability, all of which typically depend on specific regulatory proteins binding to an mRNA. In eukaryotes, non-translating mRNPs often assemble together into visible cytoplasmic structures that lack a limiting membrane, termed mRNP granules. Specific examples of these include P-bodies,[1,2] stress granules,[2,3] germ granules,[4] and neuronal transport granules[5] (**Fig. 1**). Recent work has uncovered much about how mRNAs are regulated within these structures, as well as how granules assemble, disassemble, and transit through cells. Importantly, mRNP granules are also strongly implicated in a variety of diseases, especially degenerative disorders, thus it is an exciting time for the field.

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Diversity and Similarity Among Different Mrnp Granule Types

Specific classification of mRNP granules depends upon their cellular context, presumed function, and the presence of particular protein markers. For instance, germ granules (subtypes of which include P-granules, nuage, chromatoid bodies, inter-mitochondrial cement, and sponge bodies) are usually defined as cytoplasmic mRNP foci present in germ cells, which often contain the RNA helicase Vasa,[4] and are implicated in storage and localization of mRNAs. The developmental stage, cellular localization, composition, and model organism studied further dictates their sub-classification.[4] In neuronal cells, transport granules are defined as cytoplasmic mRNP foci that transit along microtubules in axons and dendrites, with presumed functions in mRNA localization, particularly in growth cones and at synapses. Subtypes are mainly defined by the presence of RNA binding proteins such as Staufen. Despite the absence of translating mRNPs, many neuronal granules also harbor ribosomes.[5] P-bodies, which are generally seen in all cell types, are defined by enrichment for mRNA decay proteins,[1] whereas stress granules normally only form during cellular stress, and contain numerous initiation factors, including small ribosomal subunits.[3] Both types are thought to contribute to regulation of translation, whereas P-bodies are also thought to function in mRNA decay.

Despite this diversity, all mRNP granules have features in common. First, they all contain repressed mRNAs that are capable of (re)-entering translation in response to appropriate signals.[6-9] Second, they share many RNA binding proteins and mRNA species in common,[10] and indeed factors concentrated in one granule often re-localize to another granule type with time or changes in cellular conditions.[11-13] Third, mRNP granules exhibit dynamic interactions with one another such as docking, fusion, or apparent

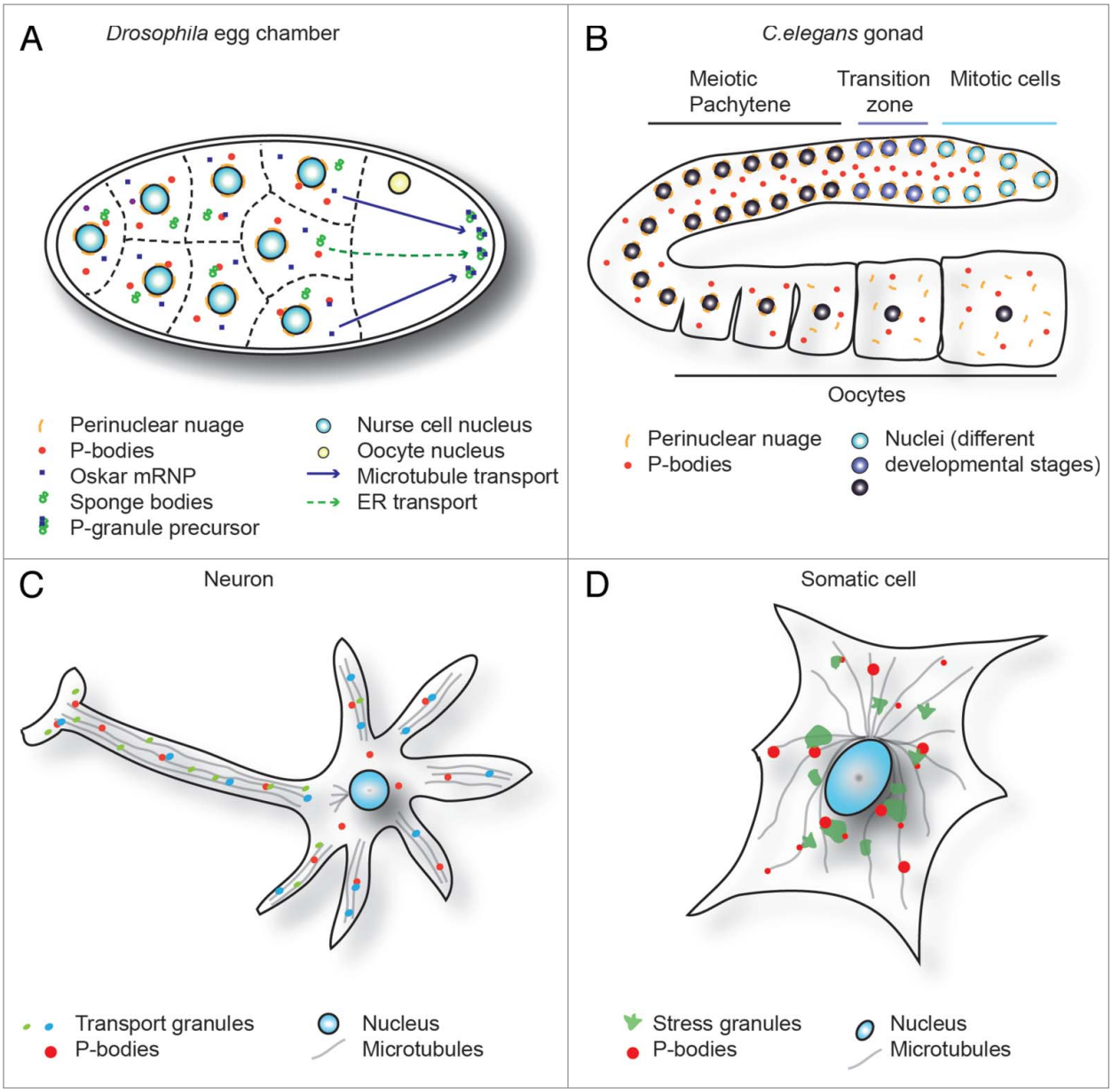

Figure 1. mRNP granules across biology. (**A**) Graphic of *Drosophila* egg chamber indicates interaction of multiple mRNP granule types in the cytoplasm of nurse cells, and modes of transport to the germ plasm. (**B**) Gonad of a *C.elegans* hermaphrodite indicates "assembly line" maturation, from mitotic stem cells at distal end (top right) to oocytes at proximal end (bottom right). P-granules remain docked with nucleus until diplotene, then re-localize to the cytoplasm with nuclear pore components. P-bodies are distributed throughout the shared cytoplasm. (Panels A and B adapted from Voronina et al., 2011 and reproduced with permission). (**C**) Simplified neuronal cell schematic demonstrating specific localization of transport granules in dendrites and the axon. Interactions with P-bodies and transport along microtubules are highlighted. (**D**) Stressed somatic cell, indicating typical distribution of stress granules (often peri-nuclear) and P-bodies, which often dock with stress granules. Interactions of both granules with microtubules also highlighted.

maturation from one granule type to the next. Examples include P-body-stress granule docking, fusion[11,14] and apparent maturation,[11,12] P-body-neuronal transport granule docking,[15] P-granule-P-body docking[16] and nuage-P-body fusion, and apparent maturation into sponge bodies.[16,17] The simplest interpretation of such observations is that mRNPs are exchanged between different granules, though this has not been directly demonstrated,[13] and remains an important unresolved issue.

mRNP Granules Assemble via Common Mechanisms

Studies of various mRNP granules types, particularly P-bodies and stress granules, have revealed common themes of assembly (**Fig. 2**). For example, non-translating mRNA is an essential component for assembly of all mRNP granules. Supporting this, P-bodies and stress granules cannot form in the presence of cycloheximide or emetine,[19,20] which traps mRNAs in polysomes. In

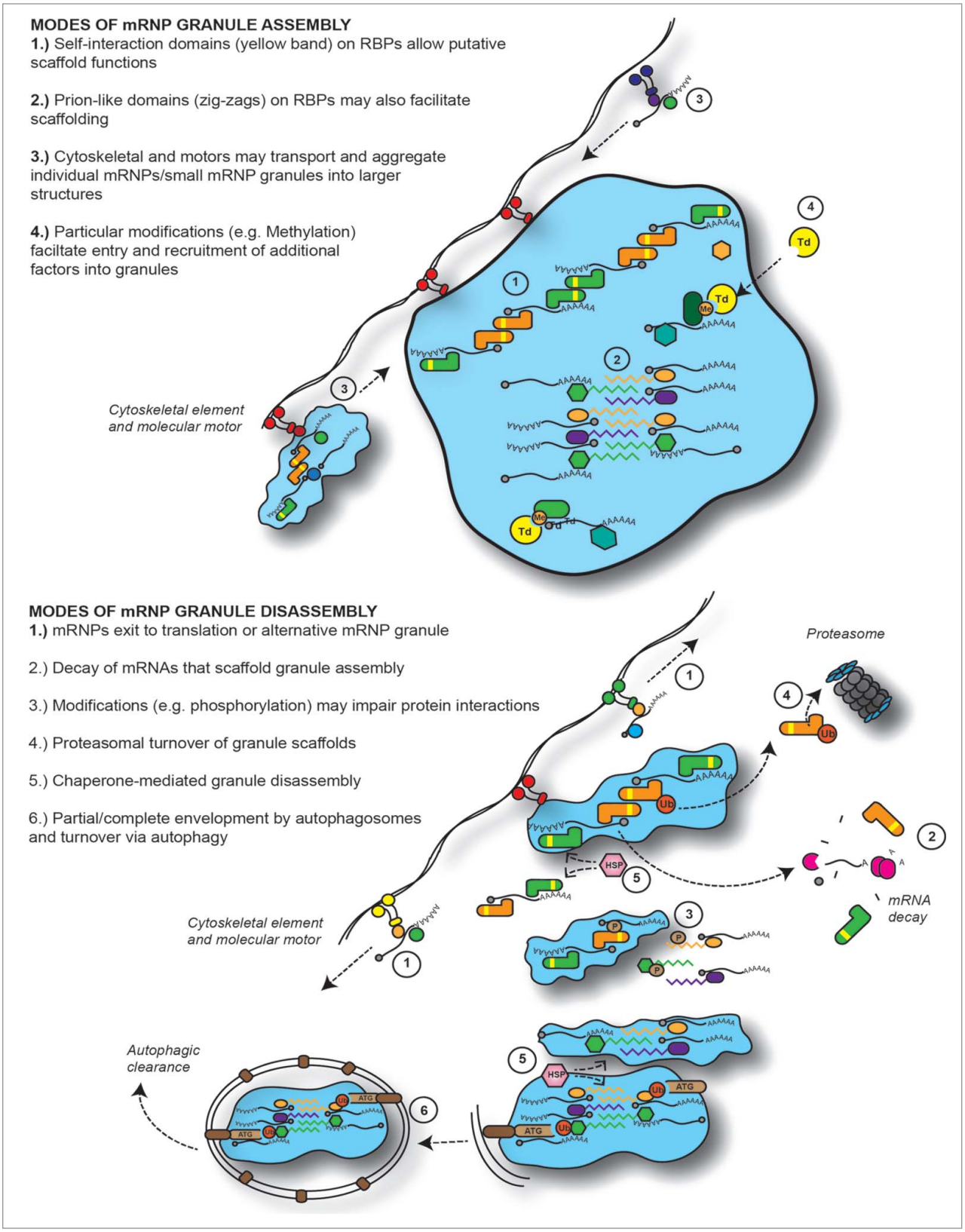

Figure 2. Modes of mRNP granule assembly and disassembly. Circled numbers refer to text in figures describing putative assembly/disassembly mechanisms of mRNP granules. Note, the use and relative importance of these likely vary depending on granule type and context. Abbreviations: RBP, RNA binding protein; Td, tudor domain protein; Me, methylation; Ub, ubiquitination; P, phosphorylation; HSP, heat shock protein; ATG, autophagy factor.

addition, perinuclear P-granules in *C. elegans* disassemble when transcription or mRNA export is inhibited.[21] Semi-purified preparations of P-bodies and neuronal transport granules are also disassembled upon RNase treatment.[21,22] Conversely, increasing the pool of non-translating mRNAs stimulates stress granule and P-body assembly, as shown by inhibition of translation initiation or mRNA decay,[20,22,24] expression of decay resistant mRNA,[22] or drugs that promote ribosome–mRNA dissociation.[11,24]

Another common assembly mechanism relies on granule proteins that harbor self-interaction domains, and thus, may potentially act as scaffolds. Clear examples of deletion of self-interaction domains impairing granule assembly include the P-granule component PGL-3,[26] the neuronal transport granule factor FMRP,[27] the P-body factor Edc3,[28] and the stress granule factor G3BP.[29] Several other granule components that contain self-interaction motifs, including Staufen[30] and Pat1,[31] also facilitate granule assembly. Consistent with a scaffold function, many of these factors also exhibit multiple direct protein interactions with other granule components.[28,31,32]

Prion-like or low-complexity domains are often found in proteins affecting granule assembly. These domains are unusually common in proteins involved in RNA metabolism, and examples of proteins whose prion-like domain contributes to granule assembly include TIA-1/Pub1 in stress granules,[12,33] and Lsm4 in yeast P-bodies.[28,34] Many more components of various mRNP granules have prion-like domains, including TIAR/Ngr1,[12,24] TDP-43,[35] FUS[36] hnRNPA2B1/A1,[37] Dhh1, Ccr4, and Pop2.[34] Recently, in vitro studies demonstrated that at sufficient concentrations, proteins containing prion-like domains such as FUS can assemble "hydrogel" structures, capable of interacting with other prion-like domains from a wide range of known mRNP granule proteins.[38] Taken together, prion-like domains may therefore be important in localization of factors to mRNP granules, as well as granule assembly. An unresolved issue is how prion interactions in mRNP granules remain apparently dynamic, reversible, and heterotypic, in contrast to the stable, homotypic prion-interactions that underpin amyloid formation in several neurodegenerative diseases (see below).

The cytoskeleton and associated motor proteins also contribute to the assembly and disassembly of mRNP granules, although effects are specific to different conditions and different granule types. For instance, microtubule depolymerizing drugs prevent assembly of large stress granules[39,40] and germ granules in early zebrafish embryos,[41] whereas P-bodies become larger, and less mobile.[42,43] Specific dynein and kinesin motor proteins also localize in stress granules, and appear to facilitate assembly and disassembly of stress granules, respectively.[40] Dynein proteins also increase P-body assembly under stress.[40] Contrasting results have been observed upon stress granule assembly following disruption of actin,[40,44] while P-body disassembly in yeast is slowed by mutation of a myosin type V protein, Myo2.[45] It is additionally very clear that localization of various germ and transport granules makes use of cytoskeletal elements for translocation and anchoring at specific sites; this subject has been well covered elsewhere.[46,47]

Protein modifications are also important in granule assembly, and recruitment of proteins to granules. For example, components of germ granules, such as Piwi-family argonautes, harbor methylated arginines that help recruit tudor domain-containing proteins. Interfering with this interaction can impair both localization of tudor-domain proteins, and the methylated proteins themselves,[48,49] as well as germ granule assembly.[50] Such interactions also underpin recruitment of tudor-domain proteins to stress granules.[52,53] O-linked N-acetyl glucosamine,[53] poly (ADP) ribosylation,[54] acetylation, and ubiquitination[39] are also modifications present on specific stress granule components, which have been implicated in stress granule assembly, albeit the mechanisms are not entirely clear. Finally, the phosphorylation of several proteins, including G3BP,[29] TTP,[55] Dcp1,[42,56] Dcp2,[57] and 4E-T[58] alters their localization within, and/or the assembly of their respective granules. In addition, phosphorylation in the prion-like domain of FUS impairs hydrogel formation in vitro.[59] Indeed, modifications have equal potential to promote disassembly, or prevent factor localization to mRNP granules[29,55] (**Fig. 2**). Modification of key mRNP granule components thus offers an appealing means to explain the dynamic assembly and disassembly of granules in response to cellular stress, developmental, or synaptic signals.

Sporadic cases of assembly mechanisms described for other RNP granules warrant more widespread investigation. For example, a long non-coding RNA termed NEAT1 underpins the assembly of nuclear paraspeckles, which are RNP granules of unknown function.[60] Interestingly, this lncRNA also binds and co-localizes in paraspeckles with TDP-43 and FUS, which are known stress granule and neuronal transport granule components. In principle, lncRNAs could help scaffold assembly of cytoplasmic mRNP granules just as mRNAs do, though examples of this are currently lacking.

Finally, intermitochondrial cement (IMC) in mouse spermatocytes may utilize organelle/molecular seeding to drive its assembly. This depends on the presence of phosphatidic acid on the surface of mitochondria. Depletion of phosphatidic acid impairs IMC formation, whereas increases in phospharidic acid drive IMC hyper-aggregation around mitochondria. Interaction of IMC components with phosphatidic acid was suggested as a means to concentrate and nucleate granule formation.[61,62] It will be interesting to determine if similar mechanisms are used by other mRNP granules.

Principles of mRNP Granule Disassembly

mRNP granule disassembly (**Fig. 2**) is thought to most commonly occur by entry of the granule mRNAs into translation. Translation typically shows an inverse relationship with stress granule and P-body numbers.[19,22] For instance, during cellular stress, bulk translation is inhibited, leading to increased granules, whereas during stress recovery, translation levels increase as granule numbers fall. This later phenomenon also holds true for specific mRNAs, which exit stress granules and enter translation during the recovery phase.[62,63] Dendritic P-bodies also

disassemble upon synaptic activation,[15] which may reflect entry of mRNAs into translation.

mRNP granules could also be disassembled via mRNA decay, which is most likely relevant to P-bodies, given their enrichment for the decay machinery, the detection of mRNA decay intermediates within, and a correlative increase in P-body numbers when hard to degrade substrates are present.[20] However, failure to degrade mRNAs due to blocks in mRNA decay also causes increases in stress granule numbers, at least in yeast,[12] which may be due to exchange of mRNPs between the two granule subtypes. Thus, mRNA decay blocks could also affect germ granules and neuronal transport granules, with which P-bodies also physically interact.[14,15] Notably, various mRNA degradative enzymes are found in mRNP granules besides P-bodies, such as Xrn1 in stress granules[11] and *Drosophila*/mouse spermatid nuage,[65] Dcp1/Dcp2 in various germ granules,[66-68] and several Argonaute proteins with endonuclease activity in stress granules,[69] and various germ granules.[70-73] Whether mRNA degradation occurs in mRNP granules besides P-bodies remains poorly studied.

Turnover of protein components, particularly scaffolding factors, could also be an efficient way to disassemble mRNP granules. Indeed, inhibition of the Ubiquitin Proteasome system induces stress granules, although this appears to be caused by activation of a GCN2-mediated stress response rather than failure to degrade stress granule assembly factors.[74] In contrast, proteasomal turnover of the helicase GLH-1 in *C. elegans* P-granules appears to be necessary to prevent excessive P-granule assembly that leads to sterility.[75] Factors associated with proteasomal function were also identified in screens for factors affecting P-granule,[76] P-body, and stress granule assembly.[77]

Chaperone proteins also affect disassembly of stress granules. Various heat shock proteins (HSPs) localize to, and affect, disassembly of stress granules in humans, flies, and yeast.[24,33,74,78] An appealing model[78] is that when cellular stress leads to accumulation of unfolded proteins, titration of HSPs would cause slower stress granule disassembly and trapping of mRNAs in non-translating states, thus helping cells conserve resources. As HSPs become available again either via increased synthesis, or from having dealt with other unfolded proteins, stress granules could once more be disassembled. However, chaperones are also implicated in P-body and stress granule assembly in inhibitor studies,[79] and not all stresses that induce P-bodies and stress granules likely lead to significant levels of protein unfolding. Therefore, the role of chaperones in mRNP granule disassembly (or assembly) is probably complex. Whether HSPs regulate germ granules or neuronal transport granules is currently unclear.

Finally, two studies have recently shown that mRNP granules can be cleared by autophagy. The first demonstrated that in *C. elegans* autophagy mutants, P-granule components erroneously formed foci in somatic cells.[80] A selective autophagy mechanism, depending on interaction of P-granule factors with the protein SEPA-1, was identified that helps clear formation of these aberrant foci.[81] Similarly, stress granules can accumulate in yeast and mammalian cell autophagy mutants, and are targeted by autophagy under various growth and stress conditions.[77] Defining the mechanism of such targeting, how mRNPs are affected, and whether autophagy contributes to the clearance of other mRNP granule types remain key issues to be addressed.

Functions of mRNP Granules

Given the conservation and utilization of mRNP granules in so many biological contexts, it is hard to imagine their assembly and form is without functional relevance. Nonetheless, identifying a role for mRNP granule assembly is not always straightforward, given the need to separate effects upon granule assembly per se from those arising from loss of a protein-specific function that directly regulates mRNAs. For instance, TIA-1 is a stress granule assembly factor,[33] but also functions in splicing regulation[82] and translation repression,[83] thus asserting that changes in mRNA translation, decay, or localization are specifically due to changes in granule assembly must be carefully scrutinized and controlled for.

With this caveat in mind, there are two fundamental reasons why granule assembly may be beneficial. First, by virtue of a higher local concentration of proteins and mRNAs, certain processes may be increased in their efficiency. To illustrate this principle, formation of Cajal bodies, which are nuclear assembly sites for small nuclear ribonuclear protein particles (snRNPs), are thought to increase snRNP assembly rates by about 10-fold.[84] Second, sequestration of proteins or mRNAs within granules may facilitate separation of processes that could interfere with one another (e.g., translation and translation repression/decay), or alter regulation of a particular process outside of the granule. Intriguing examples of the latter, unrelated to direct regulation of mRNPs, concerns localization of signaling factors in stress granules. Specifically, localization of factors such as RACK1,[85] TRAF2,[86] and TORC1[87,88] in stress granules affects signaling outcomes in response to cellular stress or extracellular signaling. However, since mRNPs form the primary component of these granules, most described or hypothesized roles have focused on possible effects on mRNA, examples of which are discussed below.

Role of mRNP Granules in mRNA Localization

Localization of mRNAs often occurs in mRNP granules. Oocytes, embryos, and neurons have proven excellent systems for study, given their highly polarized nature, although important insights have also been gained in yeast through study of the Ash1 "locasome,"[89] an mRNP granule in which Ash1 is transported to the bud tip of daughter cells during cell division. The importance of mRNA localization has been illustrated in many contexts, and a striking example of its pervasiveness is the fact that 71% of 3370 mRNAs whose localization was studied in *Drosophila* embryos showed distinct localization patterns, often mirrored by the localization of their encoded proteins.[90]

A recurring theme of mRNA localization is that mRNAs, usually by virtue of several *cis* sequences or "zipcodes," are bound by proteins that package the mRNA into translationally repressed

mRNPs, often prior to nuclear export. Next, repressed mRNPs are typically localized to and anchored at particular cellular location via interactions with molecular motors and cytoskeletal elements, although sponge bodies are thought to move along ER membranes.[18] A signaling event often precedes the switch of localized mRNAs from repression to translation, followed by granule disassembly.[9,15,91] This topic has been well covered elsewhere,[92] thus the focus here will be on how granule formation may contribute to localization.

First, it is important to note that a broad range exists in terms of how many mRNPs are actually packaged and transported in a given granule. Some of the earliest attempts at purifying nuclear transport granules identified large complexes (>1000S), with presumably multiple mRNAs.[23] Staining with in situ probes against common leader sequence or poly-adenylated mRNAs also suggest a large population of mRNAs reside in germ granules,[92,93] as well as P-bodies and stress granules.[24,25] Approaches using specific mRNA labeling also shows co-migration of several mRNA species in neuronal granule subtypes,[95] and the Ash1 locasome in yeast,[96,97] and many mRNA species individually localize in stress granules or P-bodies under identical conditions.[98,99] In contrast, recent quantitative imaging approaches in neurons indicates that some mRNA species can transit in granules or "particles" harboring just a single mRNA molecule.[100-102] Why such variation in mRNP content occurs is unclear, but presumably reflects a differential requirement for the specificity of localizing individual mRNPs to particular cellular compartments under various conditions.

Localizing multiple mRNAs together in a single granule could be beneficial in allowing coordinated regulation of multiple mRNAs with related function. Supporting this, several mRNAs harboring identical *cis* regulatory elements can co-localize in particular transport granules.[95,103] This might allow bursts of synthesis of several proteins with related function to locally respond to rapid signals that occurs at neuronal synapses. Grouping mRNPs in a single particle might also be more energy efficient in that fewer interactions with factors mediating transport (e.g., motor proteins) may be necessary, and maintenance of mRNPs in a repressed state might be facilitated by a higher local concentration of repressor proteins. However, neither of these ideas has been rigorously examined. In contrast, an obvious advantage of localizing mRNPs individually is greater specificity of control of mRNA function.

In principle, a hybrid of these approaches may be utilized, where mRNPs remodel between shared granules or individual mRNP particles, dependent upon the nature of the mRNP, cellular conditions or the localization status of the mRNP. Indeed, a recent study in live mouse neurons shows evidence of Beta-actin mRNPs being transported in granules harboring progressively fewer individual mRNPs, as distance from the soma increased.[101] mRNP density in transport granules also decreased in this[101] and another study following neuronal stimulation.[100] Such factors might explain the large diversity in data observed in neurons, where it is also possible that neuronal granule mRNPs are exchanged with P-bodies under various conditions.[15] Continued analysis at the single molecule level, ideally with multiple mRNPs in parallel, may help better understand this issue.

A key principle put forth for mRNP granules that have a primary function in localization (e.g., germ granules, neuronal transport granules) is that their mRNAs remain stable and non-translated until correctly localized. However, ribosomes are a component of many neuronal transport, and decay factors are also often found in neuronal and germ granules,[104] and sometimes are even required for their localization.[67] Thus, one assumes that the mRNP state within these granules is carefully regulated. Why transport factors involved in processes that are normally suppressed during localization? Regarding translation factors and ribosomes, one possibility is that their co-transport may aid rapid entry into translation upon arrival at their correct destination and following appropriate signals. As for decay factors, their presence may ensure that incorrectly localized mRNAs, which could be deleterious, are rapidly degraded as part of a recently theorized mis-localization quality control process.[105]

Role of mRNP Granules in Translational Control

Translation of mRNAs is highly regulated, with many mechanisms described that affect the ability of ribosomes to bind mRNAs, assemble productive initiation complexes,[106] elongate through open reading frames and recycle efficiently.[106,107] Broad translational control mechanisms that likely act upon most mRNAs include phosphorylation of the initiation factor eIF2α by various stress-responsive kinases,[109] which limits levels of ternary complex, and thus, translation initiation rates. This event facilitates assembly of stress granules under most (but not all) circumstances.[3] Another broad control mechanism is sequestration of the mRNA cap binding protein eIF4E by 4E-binding proteins (4E-BPs), a process largely regulated by the TOR signaling pathway, which integrates many growth factor and nutrient signals in order to regulate general protein synthesis rate.[106] 4E-BPs localize in P-bodies and stress granules, as does TORC1 itself (the main TOR kinase complex).[87,88]

More specific regulation of mRNAs usually involves proteins that bind *cis* elements in particular mRNAs, which then directly, or via recruitment of additional factors, disrupt the formation of productive initiation complexes. A common mechanism is impaired assembly of the eIF4E-eIF4G cap-binding complex, which facilitates recruitment of small ribosomal subunits to mRNAs.[106] Another target of translational control is poly(A) tail length. mRNAs containing short poly (A) tails are translational impaired, which may reflect an inability to bind poly(A) binding protein, which facilitates eIF4G recruitment.[110] Cytoplasmic Polyadenylation Element Binding Protein (CPEB) is a protein which can target both these steps, and which localizes in P-bodies, stress granules,[111] germ granules,[112] and neuronal transport granules.[5] Specifically, CPEB binds to mRNA 3′UTRs harboring Cytoplasmic Polyadenylation Element (CPE) cis sequences and recruits Maskin, which binds and sequesters eIF4E. CPEB also recruits deadenylase enzymes to maintain short poly(A) tails. Further details of this mechanism, and the means by which

CPEB also governs translational activation in response to appropriate signaling events has been excellently described elsewhere.[113]

Another prevalent and emerging mode of translational control is that enacted by miRNAs. These short oligonucleotides, in association with Ago proteins, form imperfect duplexes with target mRNAs, and recruit additional factors such as GW182 to form an RNA-induced silencing complex (RISC). While controversial as to which mechanism predominates, studies suggest that RISC can inhibit translation initiation, elongation, and promote deadenylation, leading to mRNA turnover.[114] Importantly, RISC components also localize in P-bodies, stress granules, germ granules, and neuronal transport granules.[115] It is likely therefore that multiple types of translationally repressed mRNPs can reside simultaneously in mRNP granules.

How might mRNP granule formation facilitate translation repression? One idea is that they may sterically restrict ribosome access; indeed the oligomerization of *oskar* mRNAs into high molecular-weight complexes by the translational repressor Bruno is thought to partially function in this manner.[116] This may apply in some cases, but cannot explain why neuronal transport granule mRNAs appear silenced, as they often contain ribosomes. A second idea is that concentration of mRNAs and translational repressors might facilitate efficient assembly or maintenance of a translationally repressed mRNP state. However, there is clear data that suggests visible granule assembly is not always important for translational repression. For example, stress granule or P-body assembly is not required to inhibit translation globally during stress responses.[12,38,39,118] Similar studies with germ granule or neuronal transport granules are currently lacking as assembly mutants that don't perturb mRNP interactions with the localization machinery, or affect translational repression directly, have not been well characterized. It thus remains unclear as to whether granule assembly is important for repression of only specific mRNAs, or whether particular granule types may function differentially with regards to translation repression.

The opposite notion, that some mRNP granules could promote translation, has also been proposed.[4,10] Just as concentration of translational repressor proteins could in principle facilitate repression, concentration of translational components, as occurs in stress granules and neuronal transport granules, might facilitate assembly of productive translation complexes, such that mRNAs rapidly enter translation in response to appropriate cues. Supporting this, polysomes can be seen via electron microscopy on the surface of polar granules in *Drosophila* germ plasm at particular developmental stages,[118] and interestingly, near the surface of P-bodies.[119] Additionally, overexpression or mutation of FUS in cell lines leads to the formation of foci resembling stress granules, which surprisingly exhibit active protein synthesis within them.[120] Such observations suggest that mRNP granules may both negatively and positively regulate translation depending on context. Therefore, careful analysis of the translational state of an mRNP granule should be verified, especially under diverse genetic or environmental conditions.

Role of mRNP Granules in mRNA Stability

Regulation of mRNA stability is a third role suggested for mRNP granules. Germ granules probably represent the clearest evidence of long-term storage or stabilization of mRNAs. For example, some mRNAs required for spermiogenesis are stored for several days in chromatoid bodies, until exiting and entering translation at appropriate developmental timepoints.[121,122] Similarly, a subtype of germ granule referred to as "storage bodies" in the *C. elegans* gonad rely on the presence of CGH-1 (homolog of the P-body factor Dhh1/RCK) for stabilization of several maternal mRNAs.[123] Stress granules and P-bodies may also harbor stable mRNAs, given that they contain mRNA stabilizing proteins such as HuR and Pab1. In addition, during stress, which induces P-body and stress granule numbers, many mRNAs are stabilized, in part by inhibition of deadenylation.[125,126] Furthermore, repressed mRNAs can localize in P-bodies for short periods of time, and return to translation upon appropriate cues or following exit from stress,[5,6] suggesting a transient storage function.

Despite this, studies utilizing fluorescence recovery after photobleaching (FRAP) indicate that most mRNP granule components shuttle in and out of mRNP granules, often quite rapidly. This is particularly true of most P-body and stress granule factors[10] (with exceptions e.g., Dcp2 in P-bodies). Germ granule components (e.g., Vasa in *Drosophila* nuage; residency time of ≈60s;[126] PGL-1 in *C. elegans* perinuclear P-granules ≈20s[21]), and neuronal granule components (e.g., Staufen in *Drosophila* neuronal granules; residency > 10 min;[104] TDP-43 in *Drosophila* neuronal granules ≈ 10s[127]) also exhibit a wide range of shuttling rates. More telling are FRAP studies on fluorescently labeled mRNAs, which have indicated that both rapidly exchanging and immobile fractions of a single mRNA species can exist within stress granules simultaneously.[12,128,129] Therefore, stress granules, and perhaps other granules, may indeed store a subpopulation of mRNAs, although at any moment, much of that mRNA species may switch to shuttling behavior, which could indicate a return to translation, or targeting to other mRNP granules. This is consistent with the previously proposed idea of stress granules as sites of mRNA triage, rather than just solely mRNA storage sites.[3]

In contrast to storage, mRNP granules may also promote decay, an idea that has only been seriously examined with P-bodies. Evidence that P-bodies can act as site of mRNA decay include the presence of all components of the 5′-3′ mRNA decay pathway, the detection of mRNA decay intermediates within P-body foci, and increases in P-body numbers when mRNA decay is inhibited at or following the mRNA decapping stage.[1,20] In addition, in *C. elegans* embryos, mature P-body assembly within somatic blastomeres correlates spatially and temporally with the degradation of maternal mRNAs.[16]

However, studies in which assembly of P-bodies or stress granules is impaired typically reveal no significant change in the stability of the mRNAs examined.[12,28,34,130] It is therefore likely that mRNA decay can proceed on individual mRNPs outside of granules. However, the studies referred to above examined only a

handful of mRNAs, thus it remains possible that specific mRNAs are reliant on assembly into P-bodies, or related structures, for efficient decay. Alternatively, granule assembly may facilitate mRNA decay only under certain conditions. Indeed, the yeast P-body assembly factor Edc3[28] was identified as a decapping enhancer in strains where decapping activity was compromised. This suggests that examining decay under conditions when decapping is limiting, which can arise for many reasons,[131] may reveal a clearer insight into the role of P-bodies in mRNA stability. The possibility of mRNA decay in other mRNP granule subtypes remains possible, but currently under investigated.

mRNP Granules and Disease

Given the wide-ranging effects mRNP granules may have on mRNA function and cell signaling, it is no surprise that mRNP granules are implicated in many diseases. For example, stress granules, P-bodies, and their components often affect, or are hijacked by RNA viruses during infection and replication (for review, see ref. 132). Stress granules are also upregulated in some cancers,[133] and may facilitate cancer cell survival.[88,134] Impaired localization of neuronal transport granules and translational control of their mRNPs are some of the mechanisms proposed to explain conditions such as spinal muscular atrophy and Fragile X syndrome (for review, see ref. 135). An area of intense recent focus however, is the emerging connection between mRNP granules and degenerative disease, which is now highlighted.

Toxic Stress Granules as a Cause of Degenerative Disease?

Recent work suggests that aberrant formation or persistence of stress granules may underpin a variety of (neuro) degenerative diseases. These include Multi-System Proteinopathy (MSP), Pagets disease, Amyotropic Lateral Sclerosis (ALS), and Frontotemporal Lobar Degeneration (FTLD). Several observations support this hypothesis. First, cells afflicted in these disease states (e.g., motor neurons in ALS) exhibit cytoplasmic foci or "inclusion bodies," which compositionally resemble stress granules. Second, many mutated proteins associated with degenerative disease are RNA binding proteins (e.g., TDP-43, FUS, SMN1, hnRNPA1, hnRNPA2, Ataxin-2, TIA-1) that localize in stress granules,[137,138] and other mRNP granule types. Third, mutated forms of these proteins often exhibit hyper-aggregative behavior in vitro and drive aberrant stress granule assembly in vivo.[37,138] Fourth, in various model systems, toxicity of exogenously expressed disease proteins is suppressed by deletion or knockdown of factors that promote stress granule assembly.[139-141] Finally, a second class of mutated proteins associated with degenerative disease are autophagy-promoting factors (VCP, optineurin, p62, ubiquilin-2[142]), which is notable given that stress granules are cleared via autophagy,[77] and cellular autophagy dysfunction is commonly observed in degenerative disease.

This data has led to a working model[136,143,144] in which aberrant formation of stress granules through granule-promoting factors (e.g., hyper-aggregating RNA-binding proteins) or failure to clear such aggregates via autophagy, leads to the persistent formation of stress granules in cells, which for some reason cannot be disassembled via other means, such as returning mRNAs to translation. One idea proposed to explain this is that the abundance of prion-like domains in stress granule components, coupled with prolonged concentration of such proteins together, eventually leads to the formation of hyper-stable amyloid-like structures that may result in stress granule being refractory to remodeling and disassembly, leaving clearance via autophagy as a last resort.[136] Supporting these ideas, ALS pathology is suppressed in model systems and patients where autophagy is upregulated,[145,146] or when stress granule assembly is impaired.[147] In addition, pathogenic forms of TDP-43 expressed in *C. elegans* or *Drosophila* show slower exchange rates from aggregates or neuronal granules by FRAP.[127,148]

Several reasons have been proposed as to why persistent stress granules or related mRNP aggregates could be toxic to cells.[136,144] Sequestration of protein factors in granules could lead to a reduced ability of granules to appropriately remodel mRNPs, and may limit the available pool of a protein that also functions elsewhere in the cell. For instance, many stress granule proteins shuttle between the nucleus and cytoplasm, and regulate processes such as splicing and export. mRNAs, and other associated mRNP factors, including miRNAs, may also be trapped in such granules, and thus, mis-regulated. Related to this, it is noteworthy that the RNA binding activity of mutant forms of TDP-43 and FUS are typically required for toxicity in model systems, even when their ability to induce aggregation is not strongly affected.[144] Specific functions of mRNP granules themselves could also be impaired. For example, disease alleles of TDP-43 impair transport along axons of particular neuronal transport granules.[149] Finally, aberrant sequestration of signaling factors in stress granules, which can alter growth and apoptotic decisions in several cases[85-88] could also be critical to disease progression. Determining the causes of cellular toxicity, and why cell types such as neurons appear especially susceptible to mutations that affect mRNP granules, are outstanding questions that now lie before the field.

Future Challenges Ahead

Several key questions regarding mRNP granules remain to be addressed. First, what is the complete RNA and protein composition of mRNP granules in their various contexts? Such knowledge would lead to insight as to both the mechanism and specificity of regulation of mRNAs within granules, as well as illuminate links to other areas of cell biology (e.g., signaling, autophagy). Second, what are the mRNP

remodeling events that govern entry and exit of mRNAs to, from, and between mRNP granules? This could shed light on a number of gene expression control mechanisms at the mRNA level. Third, how do granules assemble and disassemble, and how are these processes affected in disease? Although much has been learned here, new mechanisms continue to arise, understanding of which could reveal novel therapeutic targets in diseases involving aberrant granule behavior. Finally, can clear direct functions be assigned to the aggregation of various mRNP granules? Identifying assembly defects that do not impinge directly on other mRNP regulatory functions, coupled with the realization that mRNA regulatory processes are often interdependent, mean this will be a challenging goal. Nonetheless, new ideas coupled with new technologies promise answers and exciting new questions in the years ahead.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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