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How stressed cells triage mRNAs

In 2005, Kedersha et al. demonstrated the dynamic interactions between cytoplasmic RNA granules.

An organism placed under stress prioritizes activities essential for immediate survival, postponing or abandoning less pressing concerns. This is true at the cellular level, too; stressed cells can modify their systems to cope with damage and even prioritize protein translation toward those genes that will help them overcome the crisis (1).

Crucial to this effort are cytoplasmic stress granules (SGs) and processing bodies (P-bodies/PBs), specialized aggregates of proteins and messenger RNAs (mRNAs) that self-assemble in response to environmental stress. SGs allow cells to sort, store, and protect mRNAs (1), whereas PBs are sites of RNA degradation (2). In 1999, Paul Anderson and colleagues at Harvard Medical School demonstrated that SGs assemble after phosphorylation of eukaryotic initiation factor 2α (eIF2α) (3), which stalls protein translation at polysomes. At the time, the genesis of PBs was less well understood, although researchers had started characterizing the composition and behavior of both SGs and PBs, and suspected the two might be functionally connected.

"We were interested in understanding the relationship between stress granules and P-bodies because we noticed that they often appeared to dock together; P-bodies would kind of decorate the surface of stress granules," recalls Anderson. Led by research associate Nancy Kedersha, Anderson's group set out to catalog the composition and behavior of these cytoplasmic particles. Their findings were reported in *JCB* in 2005 (4).

Kedersha et al. first investigated what types of stressful stimuli can prompt formation of SGs and PBs in mammalian cells. Mitochondrial poisons or heat shock induced formation of SGs but not PBs, whereas oxidative stress caused the appearance of both structures. All three of these stressors induce phosphorylation of eIF2α, explaining why they prompted SG formation. However, PBs were not dependent upon eIF2α phosphorylation; PBs could even appear in cells expressing a non-phosphorylatable version of eIF2α, in which SG formation was completely disabled. Therefore, SGs and PBs form in response to different stress stimuli, and, in mammalian cells, form independently of each other.

For further insights into SG and PB function, Kedersha et al. examined what proteins were present in these two structures. As expected from previous studies, the authors found that some proteins were exclusive to each type of particle. Surprisingly, however, the structures also held some proteins in common. For example, eIF4E, a protein that assists protein translation by protecting the 5′ end of mRNAs from exonucleases, was present in both SGs and PBs. Interestingly, though, eIF4G, which binds to eIF4E during protein translation and circularizes mRNAs, was present in SGs but not PBs.

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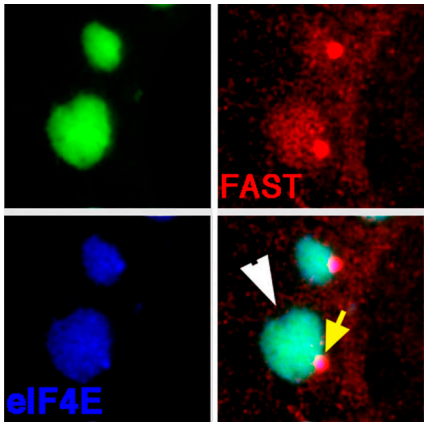
"This suggested that the pathway an RNA takes into a P-body was different than that which takes RNAs into the stress granule," says Anderson. Whereas mRNAs traffic to SGs in response to inhibition of protein translation, access to PBs may involve breaking up circularized mRNAs. However, although the requirements for mRNA entry into SGs and PBs differed, it was also clear that the two structures interacted in an interesting fashion. Using immunofluorescence to stain for proteins exclusive to each structure, Kedersha et al. observed that PBs decorated SGs in cells subjected to oxidative stress.

"One obvious possibility was that if the untranslated RNAs that accumulated in the stress granules were destined for degradation, they might be transported to the P-body via these interactions," Anderson says.



Some proteins are exclusive to SGs (G3BP; green), some to PBs (FAST; red), and some are common to both (eIF4E; blue).

Consistent with this idea, the authors found that overexpression of proteins known to promote RNA decay increased SG–PB interactions. Further, certain RNAs were present in both structures.

Just as association between SGs and PBs is dynamic, so is their composition. When the researchers examined the behavior of fluorescently tagged SG and PB proteins, they observed that some components were stably associated with the structures. These likely serve some scaffolding function. However, others were only briefly present, suggesting cells might have the capacity to adjust both the protein and RNA complements of these structures on the fly. Notes Anderson, "Since stress granules are in equilibrium with polysomes, this raised the possibility that cells can regulate rates of translation and storage of RNAs by shuttling ribonucleoprotein complexes between stress granules or P-bodies and polysomes."

The proteins and pathways that regulate the dynamic relationship between PBs and SGs are a hot topic among researchers in the field today—including Kedersha and Anderson (5), who remain a team and still publish together frequently.

1. Kedersha, N., and P. Anderson. 2002. *Biochem. Soc. Trans.* 30:963–969.
2. Sheth, U., and R. Parker. 2003. *Science*. 300:805–808.
3. Kedersha, N.L., et al. 1999. *J. Cell Biol.* 147:1431–1442.
4. Kedersha, N., et al. 2005. *J. Cell Biol.* 169:871–884.
5. Ohn, T., et al. 2008. *Nat. Cell Biol.* 10:1224–1231.