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It's all about the process(ing): P-body granules & the regulation of signal transduction

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Abstract

The eukaryotic cell is subdivided into distinct functional domains by the presence of both membrane-bound and membraneless organelles. The latter include cytoplasmic granules, like the Processing-body (P-body), that are induced in response to stress and contain specific sets of mRNAs and proteins. Although P-bodies have been evolutionarily conserved, we do not yet understand the full extent of their biological functions in the cell. Early studies suggested that these structures might be sites of mRNA decay as the first protein constituents identified were enzymes involved in mRNA processing. However, more recent work indicates that this is not likely to be the primary function of these granules and has even suggested that P-bodies are sites of long-term mRNA storage. Interestingly, P-bodies, and other ribonucleoprotein granules, have been found to also contain a variety of signaling molecules, including protein kinases and phosphatases key to the normal control of cell growth and survival. Therefore, P-bodies could have a role in the modulation of cell signaling during particular types of stress. This review discusses both the general implications of such a proposal and one particular example that illustrates how the granule recruitment of a protein kinase can impact overall cell physiology.

Keywords

Processing-bodies; signal transduction; meiosis; Hrr25/CK1 protein kinase; mRNA storage; membraneless organelles; neurodegenerative disease

Membraneless organelles and cell compartmentalization

The eukaryotic cell is subdivided into functional domains by a number of well-characterized membrane-bound organelles. Developing a better understanding of the functions and biogenesis of these compartments has been a long-standing goal of cell biologists. However, it is becoming increasingly clear that there are additional levels of compartmentalization present and that these cells also contain many organelles that lack a limiting membrane. These latter structures are known by a variety of names including membraneless organelles, biomolecular condensates and assemblages (Alberti and Carra, 2018; Banani et al., 2017;

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Boeynaems et al., 2018; Toretzky and Wright, 2014). Although these compartments likely serve similar roles in the cell, the lack of a surrounding membrane allows them to be more dynamic than their membrane-bound counterparts. For example, these membraneless structures can assemble and disassemble rapidly in response to particular stimuli and the constituents within are able to exchange readily with the surrounding environment (Hyman et al., 2014). These compartments have also been found to exhibit liquid-like behavior and to form as a result of phase transitions that occur when particular constituents are concentrated at discrete sites within the cell (Banani et al., 2017; Brangwynne et al., 2009; Brangwynne et al., 2011; Hyman et al., 2014; Weber and Brangwynne, 2012). The latter process is often referred to as liquid-liquid phase separation (Hyman et al., 2014). Despite this apparent novelty, several of these membraneless structures, including the nucleolus and centrosome, have been studied for decades. However, most have been identified more recently and we are just beginning to define the mechanisms underlying their assembly and the functions that they perform in the cell. This review focuses on one particular type of membraneless organelle, a cytoplasmic granule known as the Processing-body (P-body), and a potential role that this structure might have in the modulation of signaling networks in response to stress.

P-bodies and mRNA decay

P-bodies are one example of a growing family of cellular granules that contain both RNA and protein constituents (Buchan, 2014; Luo et al., 2018; Thomas et al., 2011). P-bodies, in particular, form when translationally-arrested mRNAs and specific proteins coalesce at discrete sites in the cytoplasm in response to particular environmental stimuli (Jain and Parker, 2013). The first proteins identified in these ribonucleoprotein (RNP) structures were enzymes that have roles in mRNA processing (Bashkurov et al., 1997; Cougot et al., 2004; Eystathioy et al., 2003; Ingelfinger et al., 2002; Sheth and Parker, 2003; van Dijk et al., 2002). These constituents include the primary 5'-to-3' exonuclease, Xrn1, and the components of the major mRNA decapping complex, Dcp1 and Dcp2. As a result of these observations, P-bodies were initially proposed to be sites of active mRNA decay (Balagopal and Parker, 2009; Eulalio et al., 2007a). However, more recent work indicates that the situation *in vivo* is likely to be more complicated and that the turnover of mRNA might not be the primary function of P-body granules. For example, no significant defects in mRNA decay were detected in either yeast or mammalian cells that were defective for P-body assembly (Decker et al., 2007; Eulalio et al., 2007b; Stoecklin et al., 2006). Moreover, several groups have reported that specific mRNAs appear to be stored long-term within these RNP structures (Arribere et al., 2011; Hubstenberger et al., 2017; Standart and Weil, 2018; Zid and O'Shea, 2014). In addition, single molecule studies that detect mRNA decay intermediates indicate that decay is occurring throughout the cell and not at discrete sites, like the P-body (Horvathova et al., 2017; Tutucci et al., 2018). Finally, studies with yeast decapping mutants indicate that mRNA decay might even be suppressed within P-body granules (Hubstenberger et al., 2017; Huch and Nissan, 2017). Although these studies do not completely rule out some role in mRNA decay, they do indicate that P-bodies might have other yet to be determined functions in the cell.

Altogether, these observations raise a number of interesting issues, two of which will be discussed here. The first of these is concerned with the other potential activities that may be associated with the P-body. In particular, we will look at how the localization of particular signaling molecules to these RNP granules might influence cell physiology. The second issue concerns the regulation of the mRNA processing activities present within P-body foci. Specifically, we are interested in how these activities might be suppressed so as to allow for the long-term storage of mRNA in these RNP structures. The following sections will examine these issues in turn.

RNP granules and the regulation of signal transduction

It is important to remember that P-bodies contain a cohort of proteins in addition to the mRNAs present. Moreover, previous work indicates that these resident proteins can have a role in dictating the biological activities of the granule. For example, P-bodies in mammalian cells have been found to contain argonaute proteins and to act as sites of miRNA silencing (Eulalio et al., 2007b). A number of signaling molecules have also been found to be associated with P-bodies, including several protein kinases and phosphatases important for the regulation of cell growth (Kozubowski et al., 2011; Mitchell et al., 2013; Shah et al., 2014; Tudisca et al., 2010; Youn et al., 2018). Although the significance of this localization is not yet clear, some insight is provided by studies with a related RNP structure, known as the stress granule (SG). SGs contain translationally-repressed mRNAs and specific proteins important for the translation of these messages (Anderson and Kedersha, 2008, 2009; Buchan and Parker, 2009). These RNP granules are therefore thought to be sites of storage for mRNAs that will be translated upon the resolution of the ongoing stress. Similar to P-bodies, SGs have also been found to contain a variety of signaling molecules. Moreover, this localization in several cases has been shown to have an influence on the signaling pathway in question (Arimoto et al., 2008; Takahara and Maeda, 2012; Thedieck et al., 2013; Wippich et al., 2013). For example, the recruitment to SGs of RACK1, a scaffolding protein necessary for the activation of the MAP kinase, MTK1, has been shown to reduce the level of apoptosis that occurs under particular stress conditions (Arimoto et al., 2008). Similarly, cells are able to avoid a TORC1-induced form of programmed cell death by recruiting Raptor, a key component of the TORC1 signaling complex, to these RNP granules (Thedieck et al., 2013). It is therefore interesting to speculate that the recruitment to P-bodies could have similar effects on signal transduction pathways in the cell.

Collectively, the above observations have led researchers to propose that RNP granules may have a general role in re-configuring cellular signaling networks during specific periods of stress (Kedersha et al., 2013; Shah et al., 2014). The recruitment of protein kinases, or other signaling molecules, to an RNP granule could impact signal transduction in a number of ways. First, the recruitment of these enzymes could lead to the formation of a novel signaling complex at the site of the granule. Recent studies have described the assembly of similar liquid-phase signaling complexes at biological membranes (Banjade and Rosen, 2014; Li et al., 2012; Su et al., 2016). One function of such a complex could be to alter signal transduction so as to allow the cell to better withstand the stress that initially triggered granule formation. Alternatively, the recruitment of a protein kinase could result in the modification, and altered biological activity, of specific protein constituents of that RNP

structure. A second possibility is that the sequestration within an RNP granule could influence signaling by effectively removing an enzyme from its normal sites of action in the cell. For a protein kinase, this would result in the decreased phosphorylation of those substrates that remain at their original subcellular locales. Finally, the localization to the P-body could serve to stabilize a signaling molecule by protecting it from the proteolytic pathways that function in the cytoplasm of the cell. P-bodies are often induced by environmental stresses that can have a negative impact on protein homeostasis. A failure to associate with the P-body could therefore result in the misfolding and/or turnover of the protein in question. Below, we discuss one particular protein kinase and how its localization to P-bodies has been shown to be critical for meiosis.

Hrr25/CK1 localization to P-bodies is required for the efficient completion of meiosis

A number of protein kinases have been found to associate with P-body granules (Shah et al., 2014). The best-characterized of these is the *S. cerevisiae* Hrr25, an essential enzyme that is the yeast ortholog of the δ/ϵ isoforms of the mammalian CK1 (DeMaggio et al., 1992). This protein kinase has conserved roles in ribosome maturation, vesicle trafficking, DNA repair, clathrin-mediated endocytosis and meiosis (Arguello-Miranda et al., 2017; Biswas et al., 2011; Ghalei et al., 2015; Grozav et al., 2009; Hoekstra et al., 1991; Lord et al., 2011; Peng et al., 2015a; Petronczki et al., 2006; Ray et al., 2008; Schafer et al., 2006). The recruitment to P-bodies requires Hrr25 catalytic activity and has been conserved from yeast to humans (Zhang et al., 2016). Interestingly, this granule localization appears to be important for the maintenance of normal levels of this enzyme in the budding yeast, *S. cerevisiae* (Zhang et al., 2018; Zhang et al., 2016). A failure to localize to the P-body results in the rapid turnover of Hrr25 in a proteasome-dependent manner (Zhang et al., 2016). This turnover appears to occur specifically in conditions that normally induce P-body formation. Importantly, this protection from degradation has physiological consequences and has been shown to be important for the efficient completion of meiosis. In particular, the association with P-bodies during the early stages of meiosis allows the cell to ensure that a critical level of Hrr25 is present for the subsequent two meiotic divisions (Zhang et al., 2018). Hrr25 activity is known to be important for several steps in the meiotic program (Arguello-Miranda et al., 2017; Hoekstra et al., 1991; Petronczki et al., 2006). Thus, in this case, the association with an RNP granule provides a safe haven for a protein that is ultimately critical for the completion of an essential developmental process.

A separate question to consider here is whether this localization to P-bodies also impacts the phosphorylation status of the normal substrates of Hrr25. In dividing cells, Hrr25 is detected at multiple locations including the Golgi apparatus, the bud neck and the spindle pole body (Lord et al., 2011; Peng et al., 2015b; Shah et al., 2014). It is likely that there are specific Hrr25 substrates present at each of these sites. However, in conditions that induce P-body formation, there is a significant redistribution of Hrr25 away from these sites and to the P-body (Shah et al., 2014; Zhang et al., 2016). This redistribution could influence the phosphorylation levels on particular Hrr25 targets and thereby have a significant impact on

cell physiology. Experiments to test this possibility should be facilitated by the availability of Hrr25 variants that are specifically defective for P-body localization (Zhang et al., 2016).

Are mRNA processing enzymes silenced within P-body foci?

The final issue to be discussed here concerns the conundrum posed by the presence of mRNA processing enzymes in an organelle that is proposed to be a site of mRNA storage. To state this in another way, how are the mRNAs in the P-body protected from the decapping and exonuclease activities present in this granule? There are a number of potential answers to this question that will each need to be examined further. For example, the mRNAs and processing enzymes could be sequestered in different locations within the granule. Consistent with this possibility, a number of studies have suggested that there may be functionally-distinct areas within RNP granules (Cougot et al., 2012; Jain et al., 2016). Alternatively, these enzymes could be inhibited in some way during their residence within the P-body. One possibility is that this inactivation could be mediated by a post-translational modification, like phosphorylation. In fact, we suggest that Hrr25 is an excellent candidate for such an inhibitory activity as this enzyme is recruited to P-bodies in all circumstances tested thus far (Shah et al., 2014; Zhang et al., 2016). Many of the other signaling molecules alluded to above are recruited to P-bodies only under certain inducing conditions. In addition, the localization of Hrr25 to these granules is as efficient as that observed for any of the so-called “core” granule components, like Edc3 and Pat1 (Zhang et al., 2016). Finally, Hrr25 may interact directly with Dcp2, the catalytic subunit of the Dcp1/Dcp2 decapping complex, and the presence of Dcp2 is required for Hrr25 localization to P-body foci (Zhang et al., 2016). As a result, it will be important to test whether Dcp2 (or another P-body constituent) is a substrate for Hrr25 and whether any identified phosphorylation affects decapping activity.

Summary

Although much of the attention to date has focused on the mRNAs resident within the P-body, the protein constituents of these RNP structures will almost certainly have an important role in defining the inherent biological activities of this granule. It is therefore essential that we identify these proteins and determine how their granule localization impacts the biology of the cell. The early work on the signaling proteins present in P-bodies and SGs offers support for the continuation of these efforts and indicates that these types of RNP granules are likely to have a role in the rewiring of cellular signaling networks in response to stress.

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