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Review

Cytoplasmic ribonucleoprotein (RNP) bodies and their relationship to GW/P bodies

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ABSTRACT

GW bodies (glycine- and tryptophan-rich cytoplasmic bodies; also known as mammalian processing (P) or Dcp-containing bodies) were described in 2002 when a human autoimmune serum was used to immunoscreen a HeLa expression library. Subsequently, many investigators have focused their attention on elucidating the components and functional relevance of this ribonucleoprotein (RNP)-containing cytoplasmic microdomain to cellular and molecular biology, developmental and pathological processes, and clinical practice. GW/P body components are now known to be involved in the post-transcriptional processing of messenger RNA (mRNA) through the RNA interference pathway, 5′ → 3′ mRNA degradation as well as mRNA transport and stabilization. It is currently thought that the relevant mRNA silencing and degrading factors are partitioned to these restricted cytoplasmic microdomains thus effecting post-transcriptional regulation and the prevention of accidental degradation of functional mRNA. Although much attention has focused on GW/P bodies, other cytoplasmic RNP bodies, which have highly specialized functions, interact or co-localize with components of GW/P bodies. These include neuronal transport RNP granules, stress granules, RNP-rich cytoplasmic germline granules or chromatoid bodies, sponge bodies, cytoplasmic prion protein-induced RNP granules, U bodies and TAM bodies. This review will focus on the similarities and differences of the various cytoplasmic RNP granules as an approach to understanding their functional relationships to GW/P bodies.

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Abbreviations: Ago2, Argonaute 2; bcd, bicoid; Ca^{2+}, calcium; cyPrP, cytoplasmic prion protein; CPEB, cytoplasmic polyadenylation element-binding protein; dsRNA, double-stranded RNA; eIF, eukaryotic translation initiation factor; Exu, Exuperantia; FMRP, fragile X mental retardation protein; GWB, glycine and tryptophan-rich cytoplasmic processing bodies; hnRNP, heterogeneous nuclear ribonucleoprotein; Hsp, heat-shock protein; HuR, Hu antigen R; IIF, indirect immunofluorescence; mRNA, messenger RNA; miRNA, microRNA; MRP, mitochondrial RNA processing; P-bodies, processing bodies; PSDs, post-synaptic densities; pre-miRNA, precursor-miRNA; PrP, prion protein; RNP, ribonucleoprotein; RISC, RNA-induced silencing complex; RNAi, RNA interference or RNA silencing; siRNA, small interfering RNA; SjS, Sjögren's syndrome; snRNPs, small nuclear ribonucleoproteins; SMA, spinal motor atrophy; SMN protein, survival of motor neurons protein; SLE, systemic lupus erythematosus; SYNCRIP, synaptotagmin-binding cytoplasmic RNA-interacting protein; TAM, temporal asymmetric MRP; TIA, T-cell intracellular antigen; TNR, trinucleotide repeat; U snRNPs, uridine-rich small nuclear ribonucleoproteins.

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1. Introduction

Historically, human autoantibodies directed to nuclear and cytoplasmic antigens have aided clinicians in the diagnosis of many autoimmune diseases and, for cell and molecular biologists, have been remarkably powerful tools to discover and understand the structure, composition and function of novel macromolecules and cellular compartments (Fritzler, 1996; Tan, 1991). These include small nuclear ribonucleoproteins (snRNPs) and components of the spliceosome, kinetochores, nucleoli, the Golgi complex and endosomes, to name only a few (reviewed in Stinton et al., 2004). Some of the target autoantigens such as Sm, U1-RNP, SS-A/Ro, SS-B/La, Hu, and Nova bind to specific RNAs, which then associate with other proteins to form macromolecular complexes that perform a variety of functions (Mansfield and Keene, 2009; Musunuru and Darnell, 2001). At the clinical interface, autoantibodies directed to Sm, U1-RNP, SS-A/Ro and SS-B/La are powerful tools to make an earlier and more accurate diagnosis and have been used to elucidate the immune aberrations and pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis and Sjögren's syndrome (SjS) (Perl, 2009; Rosen and Casciola-Rosen, 2009).

GW bodies (GWB, glycine- and tryptophan-rich cytoplasmic processing bodies; also known as mammalian processing (P) bodies or Dcp containing bodies), hereafter referred to as GW/P bodies, were initially identified through the use of human autoantibodies that produced a unique cytoplasmic discrete speckled staining pattern on human tissue culture cell lines (Eystathioy et al., 2002). Since then, many investigators have focused their attention on elucidating the protein components of GW/P bodies as an approach to understanding their structure and function. Of these GW/P body protein components, autoantibodies to GW182/TNRC6A, GW2/TNRC6B, GW3/TNRC6C, Ge-1/Hedls/RCD8, LSm1-7, Ago2/EIF2C2, RAP55/LSm14A, and diacyl-phosphatidylethanolamine have been clinically correlated with autoimmune diseases that include idiopathic ataxia, motor and sensory neuropathy, SjS, SLE, rheumatoid arthritis and primary biliary cirrhosis (Bhanji et al., 2007; Bloch et al., 2005; Eystathioy et al., 2003b; Jakymiw et al., 2006; Laurino et al., 2006; Marnef et al., 2009; Yang et al., 2006; Yu et al., 2005). Of relevance to cell and molecular biologists, GW/P body components are involved in the post-transcriptional processing of messenger RNA (mRNA) through RNA interference (RNAi) or RNA silencing pathways (Jakymiw et al., 2005; Liu et al., 2005a,b; Pillai et al., 2005; Rehwinkel et al., 2005; Sen and Blau, 2005), 5′ → 3′ mRNA degradation (Andrei et al., 2005; Bashkirov et al., 1997; Cougot et al., 2004; Eystathioy et al., 2003c; Fenger-Gron et al., 2005; Ingelfinger et al., 2002; Rehwinkel et al., 2005; Sheth and Parker, 2003; van Dijk et al., 2002), and mRNA transport and stabilization (Barbee et al., 2006; Moser et al., 2007).

RNAi is a key pathway involved in the post-transcriptional silencing of >50% of all mRNAs in a variety of organisms (Friedman et al., 2009) and is mediated by endogenous double-stranded RNA (dsRNA) precursors termed pre-miRNA that are rapidly processed into microRNA (miRNA) duplexes of 18–22 nucleotides in length by Dicer, a dsRNA-specific endonuclease (Meister and Tuschl, 2004). RNAi can also be mediated by exogenous dsRNA that is rapidly processed by Dicer into small interfering (siRNA) duplexes of similar length (Meister and Tuschl, 2004). These small RNA duplexes are then incorporated into the RNA-induced silencing complex (RISC) where the passenger RNA strand is dissociated by cleavage, degradation or a bypass mechanism (Matranga et al., 2005). The remaining guide RNA strand subsequently activates the RISC by interacting with Argonaute 2 (Ago2), one of four Ago proteins (Ares and Proudfoot, 2005; Liu et al., 2004). The RISC then recruits one or more heteromeric protein complexes (e.g. GW182 and RCK/p54) to associate with the mRNA leading to the formation of the ribonucleoprotein (RNP) structure known as GW/P bodies. Depending on the degree of complementarity between the guide-strand miRNA or siRNA and its target mRNA, this augmented RISC then initiates post-transcriptional inhibition of gene expression through cleavage or translational repression (Eulalio et al., 2009d; Jakymiw et al., 2007). The 5′ → 3′ degradation of targeted mRNA by XRN1 exonuclease is initiated after the poly(A) tail is shortened by the deadenylase CCR4 and removal of the 5′ cap by decapping factors that include the LSm1-7 ring and the Dcp 1/2 complex (Behm-Ansmant et al., 2006; Eystathioy et al., 2003c; Rehwinkel et al., 2005). While some evidence suggests a central role for GW/P bodies in RNAi, other studies have shown that the process of active RNAi can occur in the absence of visible GW/P bodies (Chu and Rana, 2006; Rehwinkel et al., 2005). In addition, it has been observed that GW/P bodies exist in the absence of active RISC, as in Dicer knockout cells (Leung et al., 2006).

In some cells, sequestration of mRNAs targeted for repression or degradation may need to be stabilized while being transported to other cellular regions. For example, neurons contain specialized regions such as axons and dendrites that can extend great distances from the cell body and, in such cells, certain mRNAs are transported to these regions and stabilized until the appropriate signal can either remove the repressor or degrade the transcript (reviewed in Bolognani and Perrone-Bizzozero, 2008). In neurons and astrocytes, stabilization and transport proteins (i.e. Hu antigen R (HuR), fragile X mental retardation protein (FMRP), heterogeneous nuclear ribonucleoproteins (hnRNPs), and Staufen often associate with GW/P bodies (Barbee et al., 2006; Moser et al., 2007) while possibly awaiting a signal to initiate mRNA degradation, repression or release of translational inhibition.

It is currently thought that silencing and degrading factors are partitioned to these specialized cytoplasmic RNP bodies to increase the efficiency of post-transcriptional regulation and to prevent the inadvertent degradation of functional mRNA. The discovery and characterization of GW/P bodies in *S. cerevisiae* (Nissan and Parker, 2008; Sheth and Parker, 2003, 2006; Teixeira et al., 2005), *C. elegans* (Ding et al., 2005; Gallo et al., 2008; Zhang et al., 2007), *D. melanogaster* (Lin et al., 2006, 2008; Miyoshi et al., 2009; Schneider et al., 2006), *H. sapiens* (Eystathioy et al., 2002, 2003c; Jakymiw et al., 2005, 2007; Li et al., 2008; Liu et al., 2005a; Moser et al., 2007, 2009; Pauley et al., 2006; Zee et al., 2008) and somatic cells from a variety of species has led to speculation that other unique cytoplasmic RNP structures may be related to GW/P bodies in cells that have specialized functions (i.e. neurons, germline cells) or in cells induced by certain stimuli (i.e. stress, prion protein). This review will discuss the key features of GW/P bodies and compare and contrast these structures with other cytoplasmic RNP-rich microdomains that include neuronal transport RNP granules, stress granules, germline granules/chromatoid bodies, sponge bodies, cytoplasmic prion protein-induced RNP granules, U bodies and TAM bodies (Table 1).

2. GW/P bodies

Distinct cytoplasmic foci were initially reported in 1997 when Bashkirov et al. (1997) examined the cellular localization of mXRN1p in mouse E10 cells by indirect immunofluorescence (IIF). Related cytoplasmic foci were rediscovered five years later when a human autoimmune serum from a patient with ataxia and polyneuropathy (Box 1) was used to immunoscreen a HeLa expression cDNA library that led to the discovery of the novel phosphoprotein named GW182, which localized to distinct cytoplasmic foci containing hDcp and LSm4 (Eystathioy et al., 2002, 2003c) (Fig. 1). These foci, initially named GW bodies, were distinct from other cytoplasmic organelles such as endosomes, lysosomes, the Golgi complex or