



Commentary

Autophagy meets fused in sarcoma-positive stress granules

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ABSTRACT

Mutations in fused in sarcoma and/or translocated in liposarcoma (FUS, TLS or FUS) are linked to familial cases of amyotrophic lateral sclerosis (ALS). Mutant FUS selectively accumulates into discrete cytosolic structures known as stress granules under various stress conditions. In addition, mutant FUS expression can alter the dynamics and morphology of stress granules. Although the link between mutant FUS and stress granules is well established, the mechanisms modulating stress granule formation and disassembly in the context of ALS are poorly understood. In this issue of *Neurobiology of Aging*, Ryu et al. uncover the impact of autophagy on the potential toxicity of mutant FUS-positive stress granules. The authors provide evidence indicating that enhanced autophagy activity reduces the number of stress granules, which in the case of cells containing mutant FUS-positive stress granules, is neuroprotective. Overall, this study identifies an intersection between the proteostasis network and alterations in RNA metabolism in ALS through the dynamic assembly and disassembly of stress granules.

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by motor neuron loss, muscle weakness, and paralysis (Bosco and Landers, 2010). The presence of protein inclusions containing specific misfolded proteins is a histopathologic hallmark of the disease and signs of proteostasis alterations are extensively described in ALS human tissue and mouse models of the disease (Matus et al., 2013). In recent years, fused in sarcoma/translocated in liposarcoma (FUS, TLS or FUS) and Tar DNA-binding protein 43 (TDP-43), two RNA metabolism-associated proteins, were identified as major components within intracellular protein inclusions in ALS autopsy tissue, thereby opening new perspectives in the field (Mackenzie et al., 2010). In this issue, Ryu et al. explored the consequences of ALS-associated mutations in FUS within the context of cellular stress response, namely the impact of this ALS-linked protein on stress granule assembly and disassembly. Stress granules (SGs) are dynamic, messenger RNA (mRNA) and protein containing foci that form in response to acute stressors, such as

oxidative stress, endoplasmic reticulum (ER)-stress, and heat shock but that disassemble once the stress is mitigated. The exact functions of stress granules are not completely understood, but these foci are thought to regulate protein expression during stress in an attempt to reestablish cellular homeostasis (Kedersha et al., 2013). A recent screen in yeast uncovered macroautophagy (here referred to as autophagy) as a key pathway governing stress granule disassembly (Buchan et al., 2013) but the role of this pathway in stress granule assembly and disassembly within neurons, the affected cell type in ALS, had not yet been investigated. The present study confirmed that the autophagy pathway is a regulatory mechanism that modulates SG formation and clearance in mammalian neurons. Importantly, autophagy appears to provide a protective effect in neurons with mutant FUS-positive stress granules. Most disease-related protein aggregates are targeted to autophagy, a catabolic route that degrades cellular components through the lysosomal pathway. These findings build on the beneficial consequences of targeting autophagy in neurodegenerative disease that have been demonstrated as a strategy for removing neurotoxic misfolded protein species (Nixon, 2013).

Protein misfolding and impairment of the proteostasis network translate into distinct perturbations to motoneuron physiology in ALS, impacting synapse function, axonal transport, redox control, and proteasome function among other cellular processes (Pasinelli and Brown, 2006). One of the salient features of ALS is the

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occurrence of protein folding stress at the ER, which is observed as one of the earliest alterations in mouse models of the disease, before motor neuron denervation (Saxena et al., 2009). ER stress triggers adaptive reactions, including the unfolded protein response (UPR) and activation of the autophagy pathway, both of which reduce the unfolded protein load and help to reestablish cell proteostasis (Hetz and Mollereau, 2014). Interestingly, in the context of ALS, ER stress can also induce the formation of SGs that contain mutant TDP-43 (Walker et al., 2013) and mutant FUS (Bosco et al., 2010). SG markers have been detected within pathologic inclusions formed by these proteins in human disease, leading to the hypothesis that SGs may in fact represent precursors to protein aggregates detected at the end stage of disease (Wolozin, 2012).

FUS and TDP-43 are DNA- and RNA-binding proteins that participate in a wide range of nuclear and cytoplasmic processes including transcription, mRNA splicing, and microRNA processing among other functions (Lagier-Tourenne et al., 2010). These proteins are predominantly expressed in the nucleus and continuously shuttle between the nucleus and the cytosol (Ayala et al., 2008; Dormann et al., 2010, 2012; Winton et al., 2008). Mutations in the genes encoding these proteins induce drastic changes to their subcellular distribution, leading to their accumulation in the form of insoluble aggregates in the cytosol (Sreedharan and Brown, 2013). This abnormal accumulation is proposed to contribute to ALS through a loss-of-function mechanism, in addition to a gain of neurotoxic activity triggered in the cytosol (Ling et al., 2013). Here, Ryu et al. studied the distribution of wild type and ALS-linked mutant FUS into SGs under conditions of oxidative stress and validated previous findings indicating an active recruitment of mutant FUS into SGs (Sama et al., 2014). In addition to these ALS-associated proteins, SGs contain translation initiation factors, small ribosome subunits, RNA-binding proteins, and repressed mRNA (Buchan and Parker, 2009). Under stress conditions that generally induce SG formation, global translation is reduced, thereby conserving energy. SGs are thought to function in the triage of repressed mRNAs, allowing for the focused translation of those proteins necessary to overcome stress (Kedersha and Anderson, 2002).

Mutant TDP-43 has been reported to accumulate into SGs in various ALS models (Colombrita et al., 2009; Liu-Yesucevitz et al., 2014; Yasuda et al., 2013). The induction of ER stress by mutant TDP-43 was recently reported to drive its accumulation into SGs, suggesting a mechanistic connection between the UPR and the proteostasis network (Walker et al., 2013). Mutant FUS also triggers ER stress (Farg et al., 2012), and cytosolic inclusions have been reported in close association with the ER and fragmented Golgi (Farg et al., 2013). Recent findings have shown that the expression of ALS-linked mutant forms of FUS (i.e., FUS^{R495X} and FUS^{R521G}) abnormally incorporate into SGs formed under conditions of oxidative stress, ER stress, and heat shock in vitro and in zebrafish models, whereas wild-type FUS is largely excluded from these structures under the same conditions (Bosco et al., 2010). Hyperosmolar stress is the only stimuli reported to drive endogenous wild-type FUS into SGs, suggesting that FUS may also play a physiological role in stress response under certain conditions (Sama et al., 2014; Sama et al., 2013). In the context of ALS, mutant-FUS proteins were shown to interfere with the dynamics of SG assembly and/or disassembly and to alter SG morphology, suggesting that the association of mutant FUS with stress granules represents a toxic event that impairs stress response (Baron et al., 2013). Remarkably, similar observations were recently reported in cells expressing ALS-linked forms of TDP-43 and Profilin-1 (Figley et al., 2014; Liu-Yesucevitz et al., 2014), suggesting that alterations in the biogenesis and/or morphogenesis of SGs may operate as a common factor driving the pathogenesis of different ALS genes. In addition, another recent study suggested that TDP-43 mutations might alter the bidirectional trafficking of RNA granules along microtubules in neurons (Alami et al., 2014).

The study by Ryu et al. provides an interesting link between autophagy and the generation of SGs containing FUS proteins. First, the authors confirmed that expression of ALS-linked FUS^{R521C} impairs the disassembly of SGs under oxidative stress conditions. They also observed that FUS-positive SGs colocalize with the classical autophagy marker LC3. Moreover, they show that autophagy manipulation can directly impact SG formation and clearance. Stimulation with rapamycin, an autophagy activator, reduced the number of SGs, including those that were FUS^{R521C} positive.

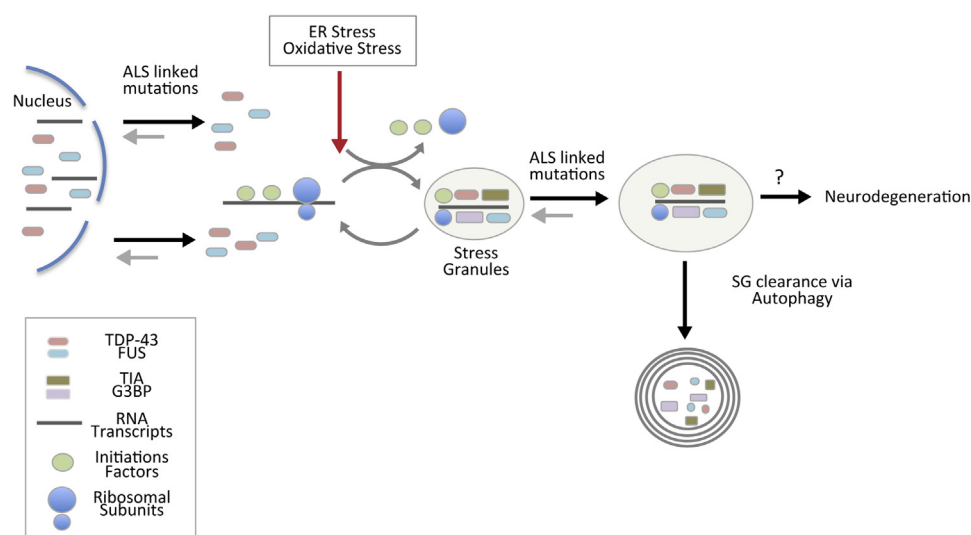


Fig. 1. The biology of stress granules in ALS. Mutations in FUS and TDP-43 in ALS trigger the mislocalization of the protein from the nucleus to the cytosol. In stress conditions, including ER and oxidative stress, protein translation is reduced, and stress granules are formed. FUS and TDP-43 are found within these cytosolic protein inclusions, an observation that may be relevant to the neurotoxic mechanisms triggered by ALS-linked mutations in these proteins. In addition, mutant FUS and TDP-43 alter the dynamics of stress granule formation and disassembly and overall SG morphology. Activation of autophagy may have neuroprotective roles in ALS by inducing the clearance of stress granules that contain aberrant ALS-linked proteins. Abbreviations: ALS, amyotrophic lateral sclerosis; ER, endoplasmic reticulum; FUS, fused in sarcoma; SG, stress granule; TDP-43, Tar DNA-binding protein 43.

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