Context-dependencontrol of stress granule dynamics

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Biomolecular condensates are de-mixed on the basis of liquid-liquid phase separation and display both compositionally and functionally peculiar compared to their surroundings. While many genetic risks in human diseases affect the material features of biomolecular condensates, multiple interventions to manipulate biomolecular condensates reversed the pathologic phenotypes, providing this new concept as attractive therapeutic targets. Stress granule (SG) is a prominent example of biomolecular condensates. SGs are unique in that they are generated in stressed cells, and they rapidly disappear when the stresses are relived. Defects in the regulation of SG reversibility are linked to the onset of several diseases including amyotrophic lateral sclerosis and frontotemporal dementia. A plethora of studies have addressed increased naked transcripts by universal cellular stresses is a critical checkpoint to build SG framework. However, how SGs are dispersed has been poorly understood. In this seminar, I will describe the recent findings about the context dependent outcome of G3BP1 ubiquitination in SG disassembly. Ubiquitination-dependent SG disassembly mechanism was observed only in heat stressed cells not in the cells affected by other stressors. Ubiquitination of G3BP1 by short or intermediate duration of heat shock exposure followed by stress removal engages ER-resident FAF2 and VCP unfoldase complex to SGs, leading to the proteasome dependent disassembly. On the contrary, SGs formed upon prolonged heat shock were poised to be eliminated by autophagy-dependent clearance machinery when heat stresses were removed. This result illustrates how cells properly process SGs to prevent the formation of aberrant SGs where proteotoxic seeds can be cultivated.