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Stress granules induced by oxidative stress in cultured fibroblast from TDP-43 mutant ALS patients

Carla Brancia[1], Paola Coni[1], Andrea Floris[2], Ilaria Bellini[2], Sandro Orrù[2] and Valeria Sogos[1]

[1] Dept. of Biomedical Sciences, University of Cagliari, 09042
[2] Medical Genetics, Dept Medical Sciences, University of Cagliari, 09126

Stress granules (SGs) are transient cytoplasmic aggregates that rapidly form when cells are exposed to stress and consist of large messenger ribonucleoprotein (mRNPs) complexes. The SGs seem to function as storage depots for translation silenced complex and are implicated in stress-induced inhibition of global protein synthesis.

Protein aggregation, has been observed in several neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS). The protein TDP-43 (TAR DNA-Binding Protein-43), encoded by one of the ALS-causative gene (TARDBP), is a major constituent of pathological inclusions in this disease and it is seems to be implicated in the regulation of SGs. Therefore we investigated the different characteristics of SGs in human cultured fibroblasts from ALS patients carrying TARDBP^{A382T} mutation (group 1) versus healthy subjects (group 2). The cells were exposed to stressful conditions using sodium arsenite (SA) at different concentrations (0.5 mM, 1 mM) and exposure times (30 min, 1h). Preliminary results showed, after 30 minutes, small and sporadic cytoplasmic inclusions immunostained for TIA-1(T-cell internal antigen-1), an early marker for SGs, in both groups of cells. After 1h, the TIA-1 immunostained granules were bright, copious and scattered into the cytosol. Interestingly, we observed a significantly higher number of cells exhibiting SGs in fibroblasts from healthy controls (66%) compared to ALS patients (34%). In parallel, we identified the RNA binding protein HuR-1 (Human antigen R) in a fraction of Tia-1 positive SGs, as well as TDP-43 localized into the nucleus of all the cells.

These data raise the possibility that TDP-43 may modulate the stress granule formation, contributing to the cellular response to acute stress. Moreover the TDP-43 may regulate gene expression as well as cellular recovery and survival, and consequently its mutation may contribute to the neurodegeneration.

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