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Abstract Title:- Paraspeckle biology in auto-regulatory protein Fused in Sarcoma associated Amyotrophic Lateral Sclerosis

Presenting author name :- Vanshika Ahuja

Presenting author institute:- Sir Ganga Ram Hospital

Co-authors name:- Sagar Verma, Shiffali Khurana, Bandana Kumari Sahu, Somasish Ghosh Dastidar, Vibha Taneja

Co-authors name institute:-Sir Ganga Ram Hospital, Bhaskaracharya College of Applied Sciences, University of Delhi, Centre of Molecular Neurosciences, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Karnataka

Aims:-Amyotrophic lateral sclerosis (ALS) is a fatal, adult-onset neurological disorder characterized by progressive degeneration of upper and lower motor neurons. Mutations in C9ORF72, SOD1, TARDBP, FUS are frequently associated with ALS. Amongst them, nuclear protein FUS auto-regulates its levels by exon skipping or intron retention mechanism. ALS-FUS mutations, especially in the Nuclear Localization Signal (NLS) are associated with cytoplasmic mis-localization of mutant protein. Furthermore, it gets sequestered in cytoplasmic stress granules and increase the production of another stress-dependent granule called Paraspeckles, in nucleus.

Methods:- Microarray data from NSC34 cells transfected with SOD1-L84F showed increased expression of FUS, another ALS-implicated gene. In addition, our lab has identified novel FUS mutations in ALS patients. Therefore, the objective of our study is to examine the formation of Paraspeckles in NSC34 and C8D1A cellular model.

Results:- Mutant SOD1 increased FUS levels in NSC34 cells, without getting mis-localized (nuclear gain-of-function). Intron retention of FUS was found to be down-regulated, directing towards impaired auto-regulatory mechanisms. Formation of Paraspeckles will be checked using cellular model. We are using novel FUS mutations identified in India and known FUS mutations to check for FUS mis-localization and paraspeckle liquid-liquid phase dynamics using co-culture and mono-culture models of NSC34 and astrocytic cell line C8D1A. Cytoplasmic mis-localization of FUS accompanied with higher levels of paraspeckle marker protein NONO were observed.

Conclusions:- Exploring SOD1 and FUS associated paraspeckle biology will give an insight of the role of Paraspeckles in ALS.

Keywords:- Paraspeckle, Sarcoma, Sclerosis