Role of hnRNP proteins in ALS

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Project duration: three years

Summary of the research project

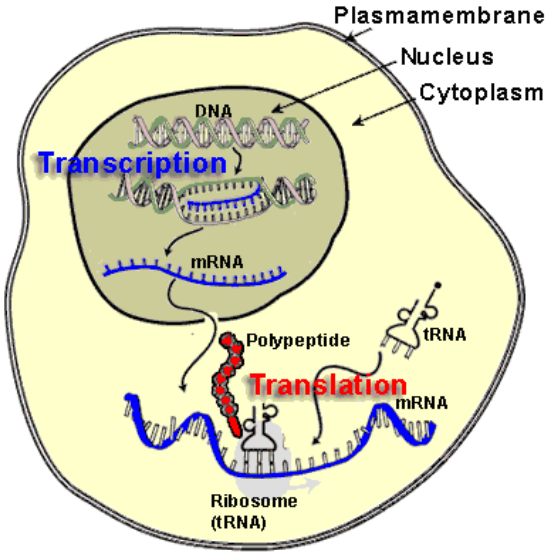
RNA was initially considered to be a passive “messenger” molecule between the information stored in the genes and the proteins produced by the cell. In recent decades, however, RNA has been increasingly shown to play a fundamental role in deciding how the basic information stored in the genes can be differentially regulated to control the complex metabolic processes of higher organisms. In particular, our brain neurons display an incredibly high level of post-transcriptional modifications at the RNA level that allows them to function properly. Recently, it has been observed that metabolic and genetic alterations in nuclear proteins that regulate RNA metabolism occur in most patients affected by ALS/FTLD.

The proteins affected in these diseases are extremely well conserved between human and flies and generally belong to the hnRNP class of RNA regulatory factors. In this project, therefore, we plan to use *Drosophila* as a model system to investigate how the most representative hnRNP proteins can affect neuronal survival and synaptic development. We will then investigate how the successful candidates interact with already known human ALS risk factors to affect disease onset and progression. Finally, the results will be validated using patient samples and human/mouse cellular and animal disease model systems. In conclusion, our project aims to better understand the general role played by hnRNP proteins in disease.

Right from the start, our results will be useful from a biomarker study point of view because they will identify modulating factors capable of affecting disease onset and progression. They will also be useful for population screening studies, to aid in the search for disease-causing mutations in the newly identified risk hnRNPs identified in the proposed study. Thirdly, this project will allow the development of novel therapeutic strategies based on antisense or small molecule technologies

Ribonucleic acid, or RNA, is a molecule that is chemically similar to DNA and carries the same code, using different bases. When DNA is biochemically "read," or transcribed, the transcription product is RNA. This RNA is read in turn, and converted into a corresponding protein.

simplified cell scheme



aimed at modifying the expression of these hnRNP proteins within neurons in order to slow down disease progression.

Emanuele Buratti is Research Scientist and Group Leader at the International center for genetic engineering and biotechnology in Trieste. He is B.Sc. in Biology and PhD in Biochemistry. Since 2009, he is contracted Professor at the University of Trieste to teach Molecular Medicine for the Biotechnology course. He is also since 2011 academic Editor at PLoS ONE and since 2012 member of the Board of Directors of the newly formed International Society for Frontotemporal Dementias.

Dr Buratti's five publications most relevant to this research are:

1) **Nuclear factor TDP-43 and SR proteins promote *in vitro* and *in vivo* CFTR exon 9 skipping.** Buratti E., Dörk T., Zuccato E., Pagani F., Romano M., Baralle F.E. EMBO Journal 2001, 20: 1774-1784.
2) **TDP-43 mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis.** Sreedharan J., Blair I.P., Tripathi V.B., Hu X., Vance C., Rogelj B., Ackerley S., Durnall J.C., Williams K.L., Buratti E., Baralle F., de Belleroche J., Mitchell J.D., Leigh P.N., Al-Chalabi A., Miller C.C., Nicholson G., and Shaw C.E. Science, 2008, 319: 1668-1672.
3) **TDP-43: gumming up neurons through protein-protein and protein-RNA interactions.** Buratti E. and F.E. Baralle. Trends in Biochemical Sciences, 2012, 37: 237-47.
4) **Autoregulation of TDP-43 mRNA levels involves interplay between transcription, splicing and alternative polyA site selection.** Avendaño-Vázquez* S.E., Dhir A.*, Bembich* S., Buratti E., Proudfoot N. and Baralle F.E. Genes & Development, 2012, 26:1679-84.
5) **Misregulation of human sortilin splicing leads to the generation of a non-functional progranulin receptor.** Prudencio M., Jansen-West K.R., Lee W.C.,Gendron T.F., Zhang Y-J, Xu Y-F, Gass J., Stuani C., Stetler C., Rademakers R., Dickson D.W., Buratti E.*, Petrucelli L.*. PNAS (USA), 2012, in press.
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