BioISI - Biosystems & Integrative Sciences Institute

Gene Expression Regulatory Networks Established by Motor Neuron disease proteins

Place of work: RNA Systems Biology Lab, Gene Expression and Regulation Group, BioISI, FCUL (Dept. of Chemistry and Biochemistry)

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Our lab has been dissecting the molecular pathways underlying the motor neuron degenerative disorders ALS and SMA using drosophila models with a focus on the orthologues of three RNA binding proteins known to be mutated in these human disorders – Caz, Smn and Tbph. As part of this work, we have generated an in-depth profile of the RNA targets of these proteins in the cell nucleus and cytoplasm using RIP-Seq, as well as a transcriptome profile of control and RNAi fly lines. In this project, the student will explore the available RNA-seq datasets to generate an in-depth understanding of the regulatory networks that depend on individual proteins, focusing on transcription, splicing and mRNA transport, translation and stability regulation. This will involve correlating the transcriptome and RIP-seq datasets to identify directly and indirectly regulated targets, characterize motifs present in these transcript populations that may correspond to protein binding sites, identify interactions with transcription factors and their downstream targets, and generate a network model summarizing the integrated dataset. Furthermore, the student will perform an in-depth exploration of splicing, transcription start-site and 3' UTR changes that occur in response to the knock-down of these proteins. This work will generate a deeper understanding of the molecular networks underlying motor neuron diseases, with the potential to uncover novel therapeutic targets.

Bibliography: Gama-Carvalho M et al (2017). Linking amyotrophic lateral sclerosis and spinal muscular atrophy through RNA-transcriptome homeostasis: a genomics perspective. J Neurochem. 141(1):12–30