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Characterization of a spinal muscular atrophy Drosophila model

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Spinal Muscular Atrophy (SMA) is a devastating rare genetic disease (1/6000) caused by loss of α-motor neurons of the spinal cord and brainstem nuclei. SMA is primarily caused by mutations in the SMN1 gene. However, as a result of a human specific duplication in the genome, the SMN locus (5q13) contains two inverted copies of SMN called SMN1 and SMN2, which are 99% identical at the amino acid level. Exon 7 of SMN1 is preferentially included giving rise to a full-length, fully functional SMN protein. However, a C-to-T transition in SMN2 promotes exon 7 skipping, which originates a truncated and less active SMN protein. The exceptional fact that a second, almost identical gene in the human genome (SMN2) has the potential of functionally complementing loss of function mutations in SMN1 provides a unique opportunity for therapeutic intervention. Indeed, drugs able to enhance SMN2 transcription or exon 7 inclusion provide proof of concept of these approaches. However, none of these experimental drugs has shown high enough activity and safety to become standard clinical practice. Thus, the identification of additional drug candidates to treat SMA is still a priority. In this project it is proposed generating a new Drosophila model of SMA based on the regulated inclusion of human SMN2 exon 7, and propose using the model in the identification of candidate drugs, as well as to understand the gene circuitry controlling SMN2 exon 7 inclusion. To achieve these long term goals it was fused SMN1 and SMN2 minigenes containing exon 7 to the luciferase reporter and have generated Drosophilatransgenics. The expression of the minigene:luc transgenes has been targeted to several Drosophila tissues and neuronal cell types with the Gal4/UAS system. In these experiments it was found that motoneuron-specific expression of both transgenes gives high (SMN1:luc) and low (SMN2:luc) luminescence readings, which is consistent with the splicing taking place in human neurons. Furthermore, these readings are very different, thus potentially offering a wide screening window. Currently, we are correlating these data with the actual use of alternative splicing sites in the SMN1:luc and SMN2:luc human minigenes in Drosophila, and plan to test whether known drugs able to enhance SMN2 exon 7 inclusion similarly promote their inclusion in our model flies.

Biography

Ruben Artero is Associate Professor of Genetics at the University of Valencia-INCLIVA Biomedical Research Institute, where he leads the Translational Genomics group dedicated to discovering mechanisms of pathogenesis of human genetic diseases as well as to design novel Drosophila models for in vivo drug discovery, particularly in myotonic dystrophy, spinal muscular atrophy and breast cancer. Before his interest in biotechnology he performed basic research in the field of developmental genetics studying Drosophila myogenesis both in University of Valencia and in the Memorial Sloan-Kettering Cancer Center (NY, USA), where he spent some six years as postdoctoral fellow. He is co-founder of the Genera Biotech company, scientific advisor of ValentiaBioPharma and inventor in four patents. He has participated in 30 international journal research publications and serves as academic editor for the PLoS ONE journal.

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