Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Exploring the contribution of transposable elements for the pathogenesis of Rett syndrome

Synopsis:

This project aims at exploring an understudied mechanism that could contribute to the etiology of Rett syndrome. Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by mutations of the MECP2 gene, located on the X chromosome. The lack of a fully functional MECP2 protein causes dysfunction of several parts of the central nervous system, affecting patients physically and intellectually. The MECP2 protein is able to bind methylated cytosines, which are usually found within the regulatory regions of genes and transposable elements. As such, MECP2 is believed to act as a transcriptional repressor in neuronal lineages. One known target of MECP2 are LINE-1 retrotransposons, the largest family of transposable elements (TEs) in mammalian genomes. Indeed, previous studies reported a higher activity of LINE-1 elements in animal models, in neurons derived from RTT human induced pluripotent stem cells (iPSCs) and in post-mortem brain samples from RTT patients. Given the importance of DNA methylation on the global silencing of TEs, it is reasonable to speculate that the influence of MECP2 on TEs might extend beyond the control of LINE-1 elements in RTT neuronal lineages; this however remains to be investigated. Moreover, whether the aberrant activity of LINE-1 is a driver or a bystander of the disease phenotype remains to be formally tested.

In this project, we will take advantage of iPSC cellular models for Rett syndrome, advanced genomic engineering and 2D neuronal differentiation to test the contribution of TEs for the pathogenesis of Rett syndrome. To address this question, we will use CRISPR-interference in RTT iPSCs to silence the expression of LINE-1 and other TEs found to be aberrantly expressed (through an ongoing bioinformatics analysis) in RTT samples. After differentiation in mature neurons, we will determine whether defects in the transcriptome and in neuronal morphology, maturation, activity and synaptic function can be rescued upon silencing of specific TE families.

Most current therapeutic approaches for RTT are centered on the re-establishment of adequate levels of functional MECP2 protein. In this project, we propose to focus on studying and correcting pathways that are downstream from MECP2. Given the growing number of studies focusing on the role of TEs in the brain, both in physiological and pathological contexts, it is likely that the misregulation of TEs impacts human pathogenesis more than previously thought. The set of approaches proposed here will allow to determine whether and how misregulated TEs impair neuronal function in RTT, which could lead to the identification of new therapeutic targets.

Supervisor: *Anne-Valerie Gendrel, Sergio de Almeida Lab, anne.gendrel@medicina.ulisboa.pt*
Webpage of the group