Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Investigating the role of LINE-1 elements in X-chromosome inactivation and gene expression through functional approaches

Synopsis:

This project aims at investigating the role of LINE-1 (L1) retrotransposons in gene regulation in the mouse. L1 elements account for a large fraction of mammalian genomes. Although most are defective, some are intact and remain genetically active and competent for their own retrotransposition. Active L1 are highly mutagenic and are therefore stringently controlled by epigenetic mechanisms. However, mobility and expression of L1 can be observed at high frequency in specific cell types or organs and during development. This, together with their non-random distribution in mammalian genomes, has led to the idea that L1 elements may have acquired some functional role in gene regulation processes, such as in the process of X-chromosome inactivation (XCI). The main objectives of this project are to investigate the contribution of active L1 to XCI, by developing functional approaches using novel genome engineering technologies. We have already generated embryonic stem cell lines where specific active L1 elements have been deleted from the X chromosome using the CRISPR-Cas9 system. One aspect of the project will involve characterizing further these cell lines to address the impact of L1 deletions on the kinetics of gene silencing during XCI, as well as the generation of new deletions using CRISPR-Cas9. A second aspect will focus on studying the effect of genome-wide repression or activation of L1 elements on XCI, monoallelic gene expression and gene expression, in both embryonic stem cells and differentiated derivatives, using CRISPR-Cas9 and high throughput sequencing approaches.

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Bibliography:

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Gendrel A-V., Attia M., Chen C-J., Diabangouaya P., Servant N., Barillot E., and Heard E. (2014). *Developmental dynamics and disease potential of random monoallelic gene expression.* Developmental Cell, 28(4):366-80.

Remunerated or volunteer training: *Volunteer*