Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Unveiling Alternative Splicing regulation of chromatin structure in cellular senescence

Synopsis:

During the cell cycle, the genome must undergo dramatic structural changes, from a decondensed, yet highly organized, interphase structure to condensed mitotic chromosomes and then back again. Mistakes in chromatin assembly and subsequent chromosome segregation can lead to diseases such as cancer, premature aging, and neurodegeneration. The tightly regulated pattern of chromatin assembly through the mitotic cell cycle requires periodic regulation of gene function at the levels of transcription, translation, protein-protein interactions, post-translational modification and degradation. However, the role of alternative splicing in the temporal control of higher-order chromatin organisation is poorly explored.

Senescent cells, which result from a stable cell cycle arrest caused by different stresses (e.g. exposure to radiation, oncogene activation, telomere erosion), have alterations in their global chromatin structure, such as the formation of condensed regions of inactive chromatin, and inducer-dependent heterogeneous transcriptomes. Since accumulation of senescent cells is associated with tissue inflammation and their elimination is an unmet clinical need, the elucidation on the specific features distinguishing different forms of senescence is crucial for the ability to therapeutically target them.

The aim of this project is to characterise cell-cycle-associated changes in the alternative splicing patterns of genes involved in the maintenance of chromatin structure, as well as differential gene expression of associated splicing factors, through a bioinformatics analysis of publicly available next-generation RNA sequencing (RNA-Seq) of HeLa cells through two continuous cell cycles. This analysis may reveal a previously underappreciated mechanism for the regulation of gene function associated to structural changes in chromatin during the cell cycle that can then be applied to further characterise chromatin and transcriptome associations in RNA-seq datasets of different senescent phenotypes. Moreover, this new perspective on chromatin structure regulation could be taken into consideration when studying genome stability and segregation, both in the context of normal physiology and diseases including cancer.

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