Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: The functions of long noncoding RNAs in maintaining telomere and genome integrity and cellular immortality

Synopsis:

Telomeres are heterochromatic structures located at the ends of linear chromosomes. Telomeres avert genomic rearrangements that may cause cancer or premature aging. Furthermore, in immortal cells, telomeres recruit DNA synthesis machineries, including the reverse transcriptase telomerase, to buffer the natural shortening of terminal DNA. The complex intertwining of telomeres with cellular functions linked to chromosome integrity, senescence and immortality places telomere biology studies at the forefront in cancer and aging research.

Human telomeres comprise repetitive DNA, the multi-protein complex shelterin and the long noncoding RNA TERRA. TERRA is transcribed from telomeres and remains associated with telomeric chromatin partly by forming DNA:RNA hybrids (telR-loops) with its template telomeric strand. We have discovered that the two shelterin factors, TRF1 and TRF2, physically bind to TERRA and functionally interact to ensure regulated telR-loop formation, through TERRA invasion of double stranded telomeric DNA. We will combine in vitro biochemistry with recombinant telomeric proteins, molecular and cellular biology and high-end microscopy to study these new interactions and their relevance in human primary fibroblasts and telomerase positive cancer cells.

We expect to generate a revolutionary picture of how the physical and functional integrity of telomeric DNA is maintained. Given the intimate connection between telomeres, cancer etiology and aging, our research should unveil novel pathways driving cellular senescence or cancer development.

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Bibliography:

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