

**TELOMERE BINDING PROTEINS TRAVEL TO NON-TELOMERIC SITES AND
REGULATE GENE EXPRESSION**

CNIO researchers discover that the telomeric protein RAP1 controls gene expression programmes through binding to non-telomeric sites

Madrid, July 11th, 2010 - Maria A. Blasco, Head of the Telomeres and Telomerase Group at the Spanish National Cancer Research Centre (CNIO), has led a study published today in the journal *Nature Cell Biology*. The study was carried out with the participation of Paula Martínez and other members of Blasco's team, as well as members of the Bioinformatics and the Genomics Core Units at the CNIO. Madalena Tarsounas and her group at the Grey Institute for Radiation Oncology and Biology in Oxford (UK) also collaborated in the study.

Shelterin is a group of six proteins (TRF1, TRF2, POT1, RAP1, TIN2 and TPP1) that form a protective shield at the ends of chromosomes or telomeres. RAP1 is the oldest protein among the six shelterins and is the only one present from yeast to mammals. However, its significance at mammalian telomeres has remained unsolved up to date. To better understand the function of RAP1, scientists in Maria Blasco's team have generated a mouse lacking the gene coding for the RAP1 protein. In contrast to mice deficient in any of the other shelterins, RAP1-deficient mice retain normal telomere function, indicating that RAP1 is non-essential for telomere protection.

The exclusive location of shelterins at the ends of chromosomes has so far remained undisputed. The CNIO study has uncovered that RAP1 is not only present at telomeres but also

all along the arms of chromosomes. This discovery has been made possible thanks to ChIP-Seq technology, which allows the genome-wide determination of *in vivo* RAP1 binding sites in the chromatin. CNIO investigators have found that RAP1 binds to extra-telomeric DNA regions by recognising at least two repeats of the telomeric sequence TTAGGG, which are present in the promoter regions of some genes as well as in inter-genomic regions.

The study demonstrates that RAP1 is not only an atypical shelterin protein because of its presence in parts of the chromosome other than the telomeres, but also, the absence of RAP1 results in changes in the expression patterns of genes involved in cancer, cell adhesion and metabolism.

With the exception of RAP1, all other shelterins are essential for mouse viability. Mice do live without RAP1, but they show shorter telomeres and develop premature hyperpigmentation of the skin, as well as metabolic problems such as obesity. This study brings the complex subject of shelterins a step closer to gene transcriptional regulation and leaves the door open for the relationship between RAP1-dependent transcriptional programmes and the cancer and ageing processes.

For the full article, please see:

<http://www.nature.com/ncb/index.html>

About the CNIO:

The Health Institute Carlos III, an institution belonging to the Spanish Ministry of Science and Innovation, established the Spanish National Cancer Research Centre (CNIO) in 1998. The mission of the CNIO is to carry out research of excellence and to offer innovative technologies within the cancer field to the Spanish National Health System. Mariano Barbacid has directed the CNIO since its inception.