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Researchers discover a new gene involved in obesity

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The discovery of an unexpected function for a gene that was associated to another process in the organism might be a solution in search of a problem, a clue to unsuspected connections. That is what has happened with RAP1, a gene that protects telomeres— the ends of chromosomes—after researchers from the Spanish National Cancer Research Centre (CNIO) surprisingly discovered its key role in obesity.

"We still don't know what evolutionary significance to attach to it, but it is at the very least interesting that a telomere gene is related to obesity", says Maria Blasco, CNIO director and co-author of the study published today in the journal *Cell Reports*.

RAP1 forms part of the shelterin complex, a group of proteins that make up the protective hood of telomeres—the DNA sequence at the ends of chromosomes that shortens with each cellular division and thus measures the ageing of the organism. There are six shelterins, and CNIO's Telomeres & Telomerase Group, which studies them in-depth, has discovered that RAP1, contrary to the rest, is not essential for the survival of the organism; but that does not mean RAP1 is not important. The reverse is rather the case: when comparing the genomes of different species, it can be observed that RAP1 is the most conserved shelterin of all. Despite the long history of evolutionary changes, RAP1 has not changed; it is present even in yeast. This normally implies an important role in the organism, but which one?

CNIO researchers had discovered that RAP1, in addition to being

located in telomeres, is also present in the rest of the chromosome; they supposed it acts regulating the action of other genes. In order to analyse this other potential function, and its importance in the organism, CNIO researchers created a lineage of mice without RAP1 and, to their surprise, discovered a model for obesity.

MICE LACKING RAP1 GAIN MORE WEIGHT

"Mice—especially female mice—without RAP1 do not eat more, but do gain weight. They suffer from metabolic syndrome, accumulate abdominal fat and present high glucose and cholesterol levels, amongst other symptoms", says Paula Martínez, first-author of the study.

The reason is that RAP1 plays an important role in the regulation of genes involved in metabolism. In particular, researchers have discovered that it acts on the same signalling pathway mediated by another protein: PPAR- gamma (PPAR-γ). In fact, PPAR-γ deficient mice suffer from a type of obesity "surprisingly similar" to that seen in mice without RAP1.

The next step in the research will be to study if RAP1 also plays a role in human obesity. "This discovery adds an element to the obesity equation, and opens up a possible new link between metabolic dysfunction and ageing, via a protein present in telomeres", says Blasco.

More information: RAP1 Protects from Obesity through Its Extratelomeric Role Regulating Gene Expression. Paula Martínez, Gonzalo Gómez-López, Fernando García, Evi Mercken, Sarah Mitchell, Juana M. Flores, Rafael de Cabo, Maria A. Blasco. *Cell Reports* (2013). doi: 10.1016/j.celrep.2013.05.030

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