Identification of a new protein essential for ovule and sperm formation

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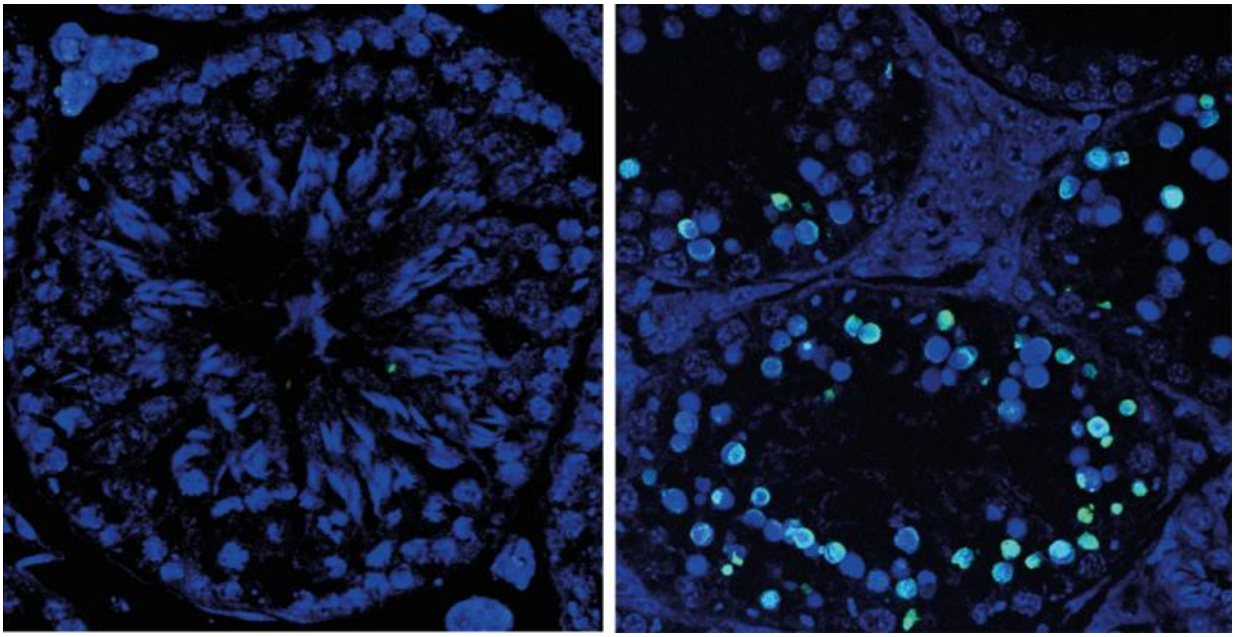


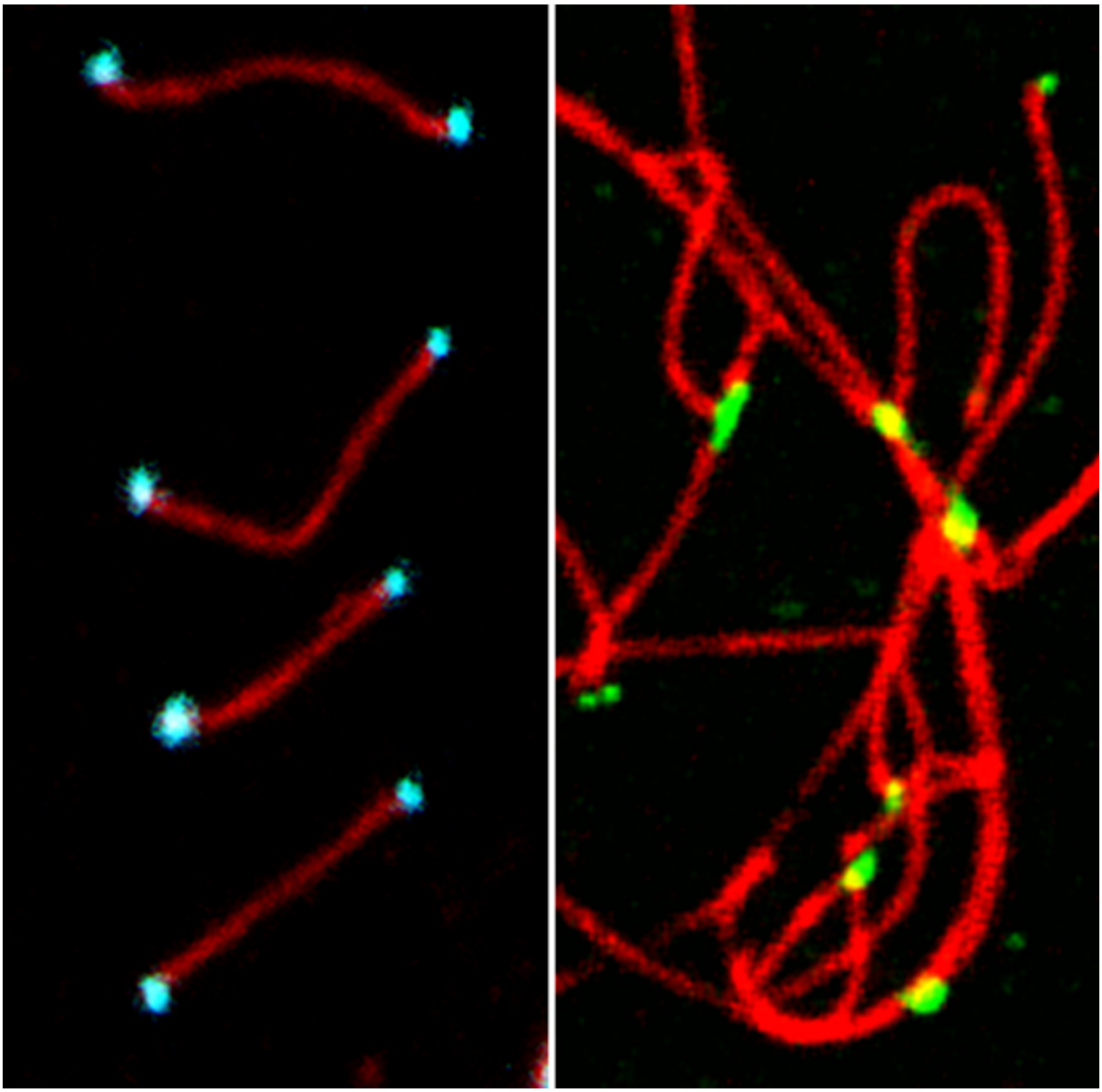
Microscopic structure of mouse testicle tissue. Left: details of health seminipherous tubule containing spermatids and sperm. Right: the tubules shrink due to mass germ cell death (in green). Credit: P. Mikolcevic, IRB Barcelona

Published today in *Nature Communications*, a study by scientists at the Institute for Research in Biomedicine (IRB Barcelona) headed by ICREA researcher Angel R. Nebreda has reported that the protein RingoA is a key regulator of meiosis—the cell division process that gives rise to ovules and sperm for sexual reproduction in mammals.

In contrast to the cells in the rest of the body, sex cells hold half the number of chromosomes (they are haploid) as a result of this special kind of cell division. In meiosis, a precursor cell —primordial germ cell— produces four spermatozoids during spermatogenesis, while only one oocyte is formed during oogenesis (the other three cells die during the process).

Mice deficient in RingoA, generated in Nebreda's Signalling and Cell Cycling Laboratory, are apparently healthy but both sexes are completely sterile. After three years of experiments, IRB Barcelona postdoctoral researchers Petra Mikolcevic and Michitaka Isoda describe the molecular imbalances that occur during meiosis as a result of the absence of this protein.

This study sheds new light on a key process for all forms of life that engage in sexual reproduction. "We all start life through meiosis so understanding how this process works is intellectually interesting," says Nebreda. Although meiosis was first described in the late 19th century, "many questions remain unanswered," explains this scientist, holder of a European Research Council grant.



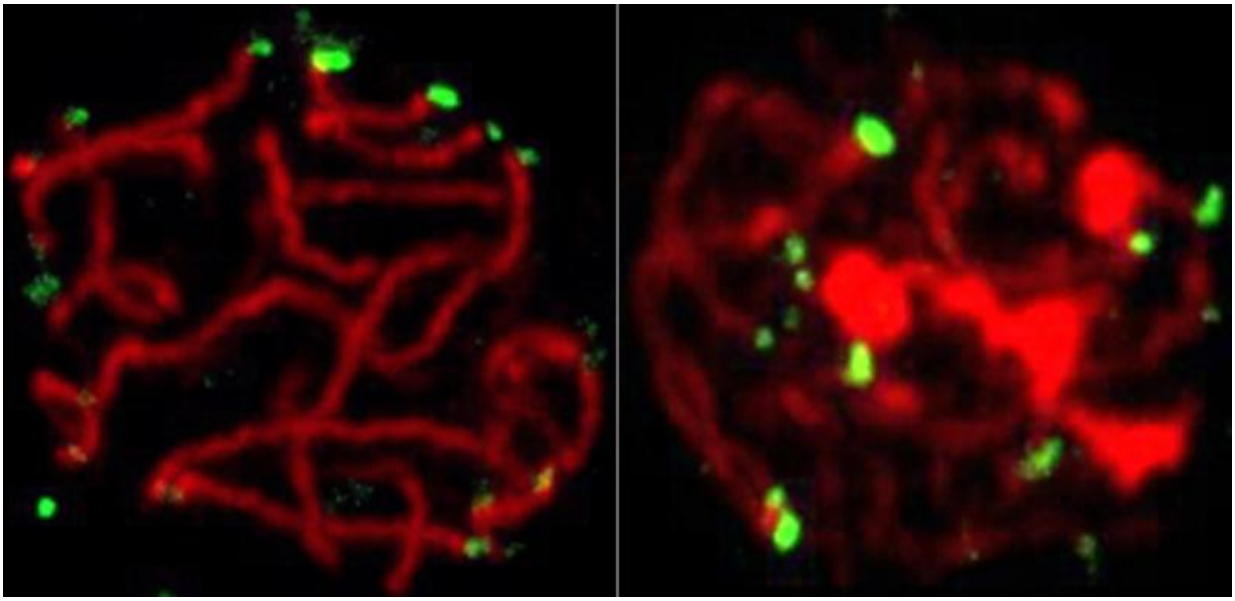
Without RingoA, telomeres (green) —the ends of chromosomes—fuse, producing impaired meiosis and cell death. When the protein is present in telomeres (blue), the chromosomes are maintained separate. Credit: P.Mikolcevic

"There are no good in vitro models available to study meiosis. It is

difficult to extract spermatocytes and to perform studies in plates; they have to be studied in the testicles. And oocytes are even worse because ovules are formed in early stages of development and working with embryos is technically complex."

RingoA and Cdk2—an essential tandem in meiosis

The scientists have discovered that RingoA is a key activator of Cdk2, the protein kinase with which it forms a complex required for meiosis. In fact, the genetic mouse model deficient in Cdk2, which was reported 12 years ago by Mariano Barbacid's group at CNIO, is also viable but sterile and shows the exact same alterations in meiosis as those observed by the researchers at IRB Barcelona.



Transversal plane of a cell nucleus. Left, the telomeres –ends of chromosomes - (in green) are attached to the nuclear membrane. In the absence of RingoA, the telomeres cannot attach well, meiosis stops and the cell dies. Credit: P. Mikolcevic, IRB Barcelona

"In biology, if two practically indistinguishable phenotypes are obtained, it is an indication that the proteins have the same function and that they may work together." What was not known until now was that RingoA is the key partner for Cdk2 in meiosis, as Cdk2 normally forms complexes with another family of proteins called cyclins.

The study demonstrates that RingoA is active at telomeres—structures that protect the ends of chromosomes and where Cdk2 is also found. During meiosis, telomeres allow chromosomes to attach to the nuclear membrane, thus allowing them to exchange DNA fragments. This recombination of chromosomes is an essential feature of meiosis.

Without the RingoA-Cdk2 complex, the telomeres of the chromosomes do not tether to the membrane but rather float in the nucleus, leading to chaotic recombination. The breaks in DNA needed for fragment exchange are not repaired and thus meiosis is not completed. Consequently, sex cells are not formed.

Male contraceptive

"It would not be unreasonable to consider the development of a male contraceptive based on RingoA-Cdk2 inhibitors," proposes Nebreda. In the same way that women produce oocytes during embryo development, men can produce spermatozoids throughout adulthood. "If the pharmaceutical industry wanted to invest in this field, we have the biochemical techniques set up for the identification of inhibitors."

More information: Essential role of the Cdk2 activator RingoA in meiotic telomere tethering to the nuclear envelope. *Nature Comms.* (2016, 30 March): DOI: 10.1038/NCOMMS11084