Sperm discovery reveals clue to genetic 'immortality'

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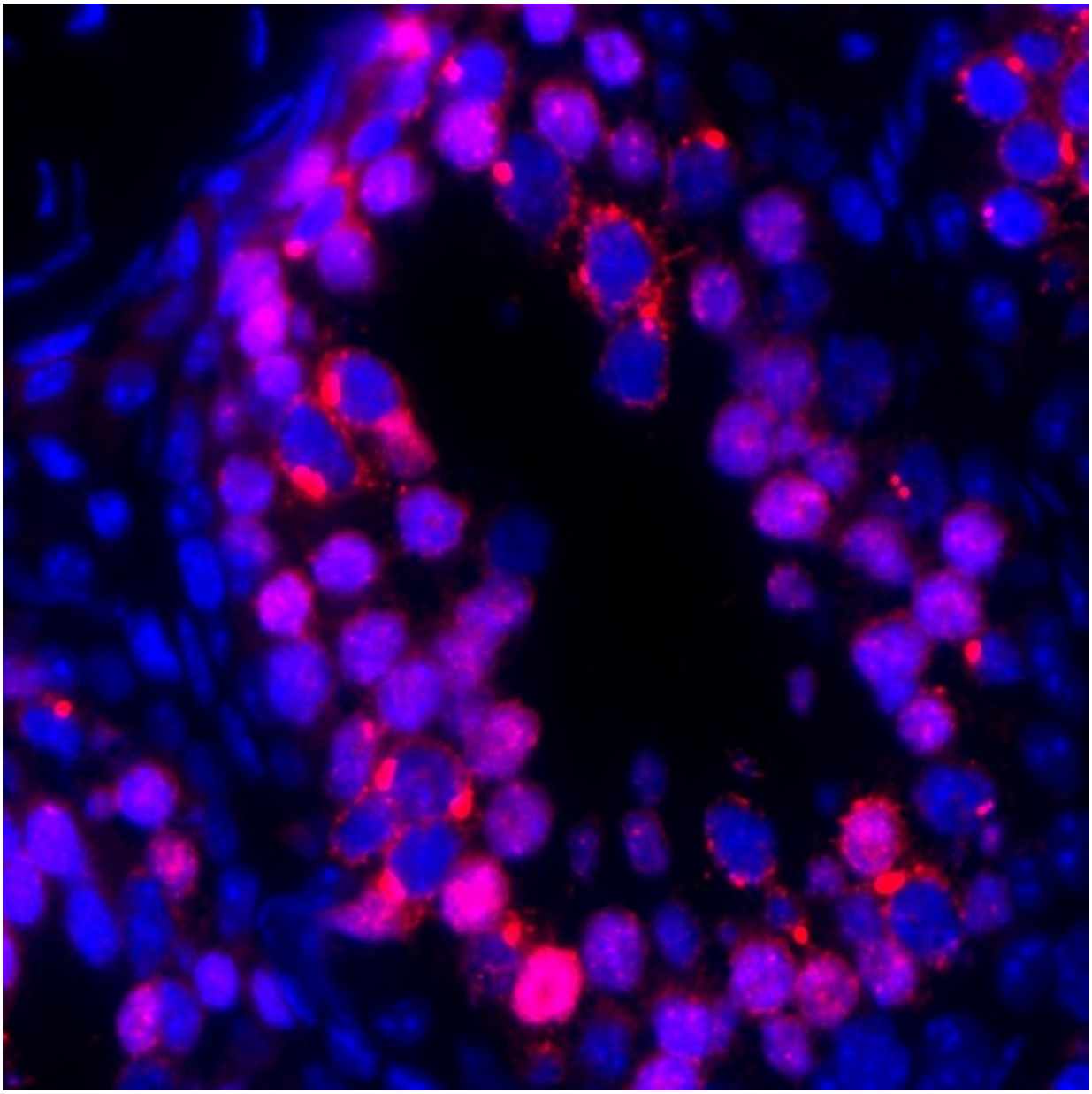

Machinery of the jumping gene LINE1 (red) mounting an attack on the DNA (blue) of germ cells Credit: Professor Dónal O'Carroll

New insights into an elusive process that protects developing sperm cells from damage in growing embryos, sheds light on how genetic information passes down, uninterrupted, through generations.

The study identified a protein, known as SPOCD1, which plays a key role in protecting the early-stage precursors to sperm, known as germ cells, from damage in a developing embryo.

During their development, germ cells undergo a reprogramming process that leaves them vulnerable to rogue genes, known as jumping genes, which can damage their DNA and lead to infertility.

"Reprogramming is essential for correct germ cell development in embryos, but leaves them temporarily vulnerable to a subset their own genes, known as jumping genes, that threaten genetic chaos." explains lead author of the study, Professor Dónal O'Carroll at the University of Edinburgh.

Evading such damage allows germ cells to become the pool of self-renewing cells that produce healthy sperm throughout adult life.

Germ cells are the vital link between generations but they need unique strategies to protect the genetic information they carry, so it can be passed successfully from parents to their offspring.

The team, led by University of Edinburgh researchers, studied the development of germ cells in mouse embryos to understand the biological pathway that protects them from jumping genes.

The study is the first to reveal the role of the SPOCD1 protein, which helps to recruit protective chemical tags, known as DNA methylations, to disable jumping genes.

Scientists have long puzzled over how germ cells escape damage during the reprogramming process, as it temporarily wipes their genetic slate clean of existing protective tags.

"The identification of SPOCD1 finally opens the doors to further investigation that will give a more elaborate understanding of this elusive process and male fertility." says O'Carroll.

Tests in male mice revealed that loss of this protein leads to infertility because the DNA methylation process does not happen correctly, allowing jumping genes to damage the developing sperms' DNA.

Jumping genes make up over half of our DNA and move around the genome controlling how our genes are used. But their activity needs to be carefully regulated to avoid them causing damage.

The team discovered that early sperm's secret line of defence is activated when SPOCD1 binds with another protein, known as MIWI2, which is already known to have a role in silencing jumping genes.

Previous studies revealed that MIWI2 protein is bound to small molecules, known as piRNAs, that play a key role in disabling jumping genes through DNA methylation.

"Our results give the first mechanistic insights into a process that is fundamental to sperm cell development and their genetic integrity." says O'Carroll.

The findings not only explain the missing part of the puzzle that allows

developing sperm to escape an early death, but also could provide insights into certain forms of infertility.

The study, published in *Nature*, was funded by Wellcome and the European Union's Horizon 2020 programme. It also involved researchers from the Universities of Cambridge, Paris and Berlin.

More information: Ansgar Zoch et al. SPOCD1 is an essential executor of piRNA-directed de novo DNA methylation, *Nature* (2020). DOI: 10.1038/s41586-020-2557-5

Provided by University of Edinburgh