Published online 7 July 2009 | Nature | doi:10.1038/news.2009.646

Sperm-like cells made from human embryonic stem cells

But results are only preliminary, researchers caution.

Heidi Ledford

PunchstockSperm cells produced from stem cells would be useful for the study of diseases.Sperm cells

Human embryonic stem cells have been coaxed into forming sperm-like cells, researchers report today1. The cells have some of the hallmarks of sperm — they can swim, for example — but require much more characterization before they can be embraced as an experimental model for the study of inherited diseases and infertility.

Meanwhile, the use of such cells to help infertile couples to have children remains a distant prospect; in several countries, including the UK, it would actually be illegal even if they were properly characterised.

With approximately one in seven couples experiencing fertility problems, there is a strong push to develop a robust method for generating sperm and eggs for research. But researchers have struggled for years to produce reproductive cells from stem cells. The task is particularly difficult because it requires a complex form of cell division called meiosis, which reduces the number of chromosomes per cell by half.

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> Renee Reijo Pera
> Stanford University School of Medicine

In addition, the DNA packaged in reproductive cells is wiped clean of a chemical modification known as methylation, which involves the attachment of methyl groups to certain regions of the genome. These modifications are then added back in patterns characteristic of either sperm or egg cells.

Methylation can affect gene expression, and if either demethylation or remethylation does not occur properly the results can be disastrous. "If these genes are not correctly modified, it's like you erased a hard drive but you didn't do it very well," says Renee Reijo Pera, director of the Center for Human Embryonic Stem Cell Research and Education at Stanford University School of Medicine in Palo Alto, California. "The embryo may develop and some offspring may be born, but there could be gross abnormalities."

Possible evidence of this was observed in 2006, when Karim Nayernia, now of the University of Newcastle Upon Tyne, UK, and his colleagues reported that they had produced sperm from mouse embryonic stem cells. When the sperm were used to fertilize mouse eggs, the few pups that were born died prematurely2. Nayernia

says his lab is still working to determine what went wrong, but early results suggest that DNA in the sperm was not properly remethylated.

From mice to men

Now, Nayernia and his colleagues have used a similar technique to create sperm-like cells from human embryonic stem cells1. The team labelled embryonic stem cells with a fluorescent marker attached to a particular gene that is expressed during reproductive-cell development, and cultured the cells in a medium that encourages differentiation into sperm cells.

About 3% of the resulting cells contained enough DNA for only one set of chromosomes, suggesting that meiosis had occurred. Some of these cells also formed tails and were motile.

The work is "a good start", says Reijo Pera, who was not affiliated with the study, but additional characterization of these cells will be needed before they can be taken up as an experimental model for the study of sperm. Nayernia and his colleagues have not yet analysed methylation patterns in their sperm-like cells, or conducted a detailed study of the cells' morphology.

Robin Lovell-Badge, head of the Division of Stem Cell Biology and Developmental Genetics at the National Institute for Medical Research in London, notes that Nayernia's team looked only at the total DNA content of the cells, and did not confirm that they contained the right number of chromosomes. "He needs to identify putative haploid cells and check they really have all 23 chromosomes and no more," says Lovell-Badge.

But Nayernia says the work is a "proof-of-principle experiment". "We don't claim that it is fully normal sperm, but they do have some of the right characteristics."

These issues would need to be carefully addressed before any attempt could be made to fertilize a human egg with the cells, but some preliminary tests of the sperm-like cells' ability to behave like sperm could be performed. For example, sperm should be able to bind to the membrane that surrounds unfertilized egg cells regardless of whether there is an egg inside, Reijo Pera notes.

Meanwhile, Nayernia and his colleagues have also launched a project to produce sperm cells from induced pluripotent stem cells, which can be generated from adult cells. Such cells would make it easier to derive sperm cells from many individuals. "Then we can, for example, see whether environmental factors or genetic factors are affecting fertility, and which step of sperm production has been affected by those factors," he says.

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References

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Published online 30 July 2009 | Nature | doi:10.1038/news.2009.753

News
Editor retracts sperm-creation paper

Plagiarism accusation hits stem-cell research.

Alison Abbott
spermA report of sperm-like cells created from human embryonic stem cells has attracted controversy.Alamy

A paper reporting the creation of sperm-like cells from human embryonic stem cells has been retracted by the editor of the journal Stem Cells and Development. The work had garnered headlines worldwide after being published three weeks ago (see 'Sperm-like cells made from human embryonic stem cells').

The journal's editor-in-chief Graham Parker says he took the radical step on 27 July because two paragraphs in the introduction of the paper, entitled 'In Vitro Derivation of Human Sperm from Embryonic Stem Cells',1 had been plagiarised from a 2007 review published in another journal, Biology of Reproduction.2

He had been alerted to the plagiarism on 10 July — three days after the article had been published online — by the editors of Biology of Reproduction. Parker says that the corresponding author, Karim Nayernia of the North East England Stem Cell Institute in Newcastle, UK, and the University of Newcastle, had failed to provide convincing evidence that the two paragraphs had been included in the submitted version of the manuscript by mistake.

The retraction has surprised even critics of the paper, who had complained that the work had been over-hyped. "If there is nothing else behind this, it seems a little harsh," says Harry Moore, co-director of the Centre for Stem Cell Biology at the University of Sheffield, UK.
Valid conclusions

The article reported that sperm precursor cells could be derived from human embryonic stem cells in vitro. These derived cells were able to divide and generate cells with just one set of chromosomes, characteristic of sperm. Although the text of the article modestly refers to these as "sperm-like cells" with "tail-like structures", its title, and the press release which accompanied its publication, refer baldly to human sperm.

"That raised hackles," says Moore. "With that claim the authors opened themselves to criticism, some of it unfair, because the paper did not in fact show that sperm had been derived."

Parker insists that there were no other problems with the paper other than the copied paragraphs. Along with five other editors of his journal, he nevertheless decided that because the paper included "an act of scientific misconduct, retraction was the correct course of action in this instance".

Nayernia declined to comment to Nature, but an official statement from the university says that the paper's original first author, Jae Ho Lee, a postdoc who has

since left the university, was responsible for the plagiarism and has apologized to the authors. "No question has been raised about the science conducted or the conclusions of the research," according to the statement. "The name of Dr Lee has been removed from the first authorship," the statement continues. "The paper will now be submitted to another peer-reviewed academic journal."

The statement also says that the "correct version of the manuscript, upon the request of the journal's editor, had been immediately submitted to the journal during the process of proof reading".

The paper had been published online 'ahead of editing' to avoid undue delay, with proofreading happening after publication to correct textual or copy-editing errors, explains Parker. "But plagiarism can come to light at any point in the publishing process," he says. "Proofing isn't a magical stage that allows authors to correct any inappropriate acts."

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