New study yields clue to how stem cells form

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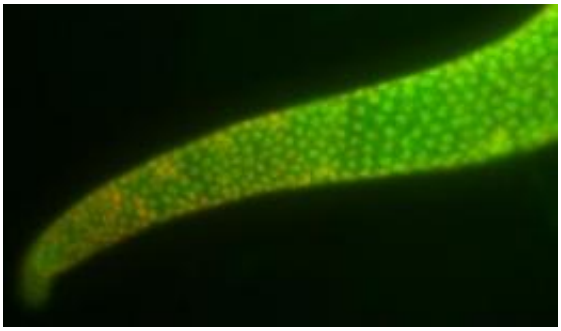

This is a KDM1 enzyme in a dissected worm gonad. Credit: David Katz

An Emory University study shows some of the first direct evidence of a process required for epigenetic reprogramming between generations - a finding that could shed more light on the mechanisms of fertilization, stem-cell formation and cloning. The journal *Cell* published the results of the study on the nematode *C. elegans* in its April 17 issue.

"We believe that we have demonstrated one of the processes that erases the information in a fertilized egg, so that the offspring can begin life with a clean slate," says David Katz, lead author of the study. Katz is a post-doctoral fellow in the lab of William Kelly, associate professor of biology at Emory and a co-author of the study.

"One of the most fundamental mysteries in biology is how a sperm and egg create a new organism. By looking at the process at the molecular level, we're gaining understanding of this basic question of life," Katz

says.

When a sperm cell fertilizes an egg cell, the specialized programming of each parent cell must be erased, in order to form a zygote that can give rise to a new organism. The process by which these two differentiated cells return to a developmental ground state in the zygote - the ultimate stem cell - is little understood.

'An amazing phenotype'

The Emory researchers wanted to test the theory that removal of a particular histone protein modification involved in the packaging of DNA - dimethylation of histone H3 on lysine 4 - is involved in reprogramming the germ line.

They compared successive generations of a normal strain of *C. elegans* - a microscopic worm commonly used for studying cell differentiation - with a mutant strain. The mutants lacked an enzyme that test-tube experiments have previously shown appears to play an "erasing" role - demethylating histones to remove information from the packaging of DNA.

In the normal strain of the worms, the histone modification the Emory researchers had targeted was not passed on to the next generation, but in the mutant strain the modification continued through 30 generations, and each generation became progressively less fertile.

"That's an amazing phenotype," Katz says. "The organism gradually lost its ability to reproduce. We have shown that when this enzyme is missing, the worms can inherit the histone modification - not only from cell to cell, but from generation to generation."

When the researchers re-inserted the missing enzyme into the sterile

generations of mutant worms, they were able to reverse the process: the worms no longer inherited the histone modification, and they regained fertility.

Showing inheritance of epigenetic event

For years, it's been accepted that histone proteins help coil six-foot strands of DNA into tight balls, compact enough to fit inside the nucleus of a cell. Histone modifications have also been known to correlate with gene expression. More recently, researchers have theorized that a chemical change in the histone packaging of DNA, known as an epigenetic event, can be passed on - just as genes themselves can be inherited.

"This study is one of the first demonstrations in a living organism that this theory may be true - that every generation can be affected by an epigenetic event," Kelly says.

"Our work provides some of the best, direct evidence that chemical modifications in the packaging of DNA can be inherited from cell to cell," Katz added. "That indicates that these chemical modifications are not just involved in packaging - they contain information."

Groundwork for stem-cell therapies

A better understanding of the role of histones, and the enzymes involved in their modification, could lead to therapies for everything from cancer to infertility. "Stem-cell therapies are an incredibly promising technology for treating any problem that has to do with defective cells," Katz says. "We're hoping that our work will help this technology to develop."

Additional authors on the Emory study were Matthew Edwards, a research specialist at Emory, and Valerie Reinke of Yale University School of Medicine.

Katz and his colleagues are now building on the results of the study, to see if a lack of the erasing enzyme shows a similar effect in mice.

Source: Emory University (news : web)