Scientists identify new way cells turn off genes

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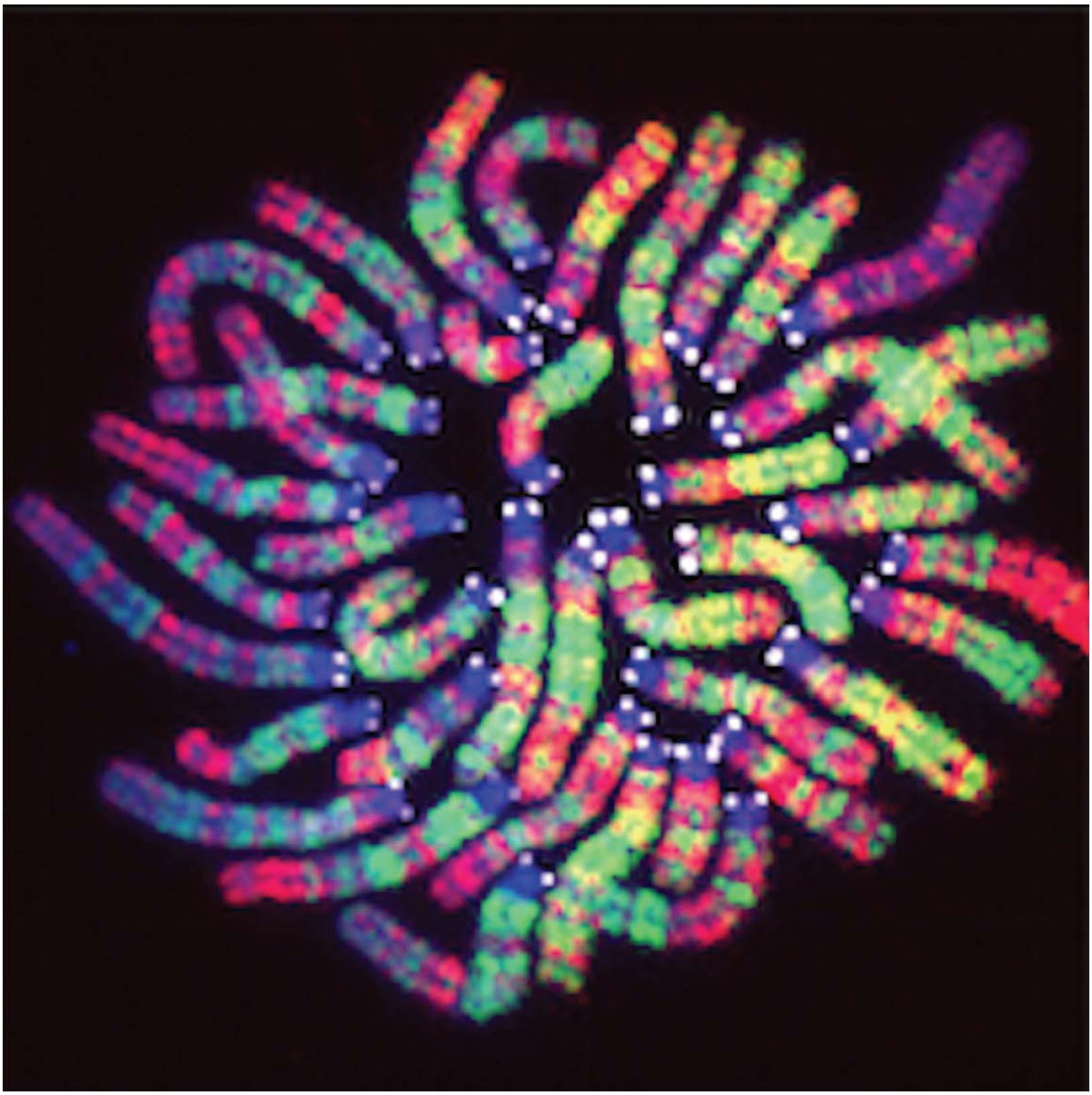

A microscopy image of the complete set of chromosomes in a 2-cell stage mouse embryo reveals chemical tags that ,decorate, DNA-packaging proteins called histones. The tag H3K27me3 (shown in green), can switch gene activity off. The tag H3K4me3 (shown in red) can turn gene activity on. White represents the chromosomes' centromeres, and blue represents DNA. Credit: Azusa Inoue and Yi Zhang

Cells have more than one trick up their sleeve for controlling certain genes that regulate fetal growth and development.

It's crucial for one copy of these genes, called imprinted genes, to be turned off in either the sperm or egg. If one copy isn't turned off, developmental and neurological disorders can occur, or cancer may strike later in life. Now, scientists have discovered a new way that cells keep these genes quiet: by chemically tagging histones - proteins that help keep DNA tightly coiled in the nucleus.

Modifying a histone called H3K27 shuts down the activity of some imprinted genes in mice, Howard Hughes Medical Institute (HHMI) Investigator Yi Zhang and colleagues report July 19 in the journal *Nature*. The finding could shed light on developmental disorders that tend to occur in children conceived with assisted reproductive technologies such as in vitro fertilization, Zhang says. It may also help explain the difficulty of cloning mammals.

The discovery of a new mechanism for shutting down imprinted genes also raises many provocative questions, Zhang says. "We believe our study will open up a new field of research."

During reproduction, humans inherit two working copies of most genes - one copy, or allele, from each parent. For a very small number of genes,

though, people inherit only one working copy; the other copy is turned off, forever silenced. This silencing, or imprinting, mechanism has long been a central focus of gene regulation research, says Zhang, a geneticist at Boston Children's Hospital and Harvard Medical School.

Since the first report of imprinted genes in mammals more than a quarter of a century ago, scientists have known of only one cellular mechanism that keeps these genes inactive - "decorating" the DNA with small molecules called methyl groups. Now, Zhang and colleagues have discovered a new way that cells can silence some imprinted genes: by adding methyl groups to histones. The research also identified 76 genes in mice that potentially belong to this class of developmental genes. Until now, roughly 150 imprinted genes have been found in mice and about half that number in humans.

Scientists know that imprinting is very old evolutionarily, and occurs in diverse organisms, from plants to humans to tigers. Imprinting, in fact, is partly responsible for the two types of offspring that can emerge when a lion and a tiger mate. If the mom is a lion, she may bear a tigon, which is often smaller than both of its parents. If the mom is a tiger, she can have a liger, a larger and stronger creature than either parent or a tigon. Differences in male and female imprinted genes among species contribute to the size differences in these two kinds of offspring.

Researchers still have much to learn about the imprinting process and the genes involved, Zhang says, but the discovery of a second mechanism for silencing one copy of these genes underscores imprinting's importance. The second silencing mechanism may have evolved as a sort of back-up plan, he says.

Imprinting gone awry can lead to problems. Because there's only one functioning allele of an imprinted gene, if that copy becomes defective, developmental abnormalities can occur. These include Angelman

syndrome, which causes learning difficulties, speech problems, and seizures. Trouble also arises when a person inherits two working copies of a gene that should be imprinted, as with Beckwith-Wiedemann syndrome, which can cause complications during pregnancy due to overgrowth of the baby, and lead to various birth defects.

In children conceived with the help of assisted reproductive technologies, scientists have seen an increase in the incidence of imprinting disorders. The reason why is unclear, but something about the process of these technologies could lead to imprinting problems, Zhang says, or perhaps the imprinting problems are related to infertility itself. He thinks a better understanding of imprinting could help scientists find ways to reduce the occurrence of these disorders.

Improper imprinting could also explain some of the difficulties researchers encounter when trying to clone mammals. Usually imprinting marks are erased in the germ cell precursor cells and then rewritten in the eggs or sperm. Previous research suggests that glitches in the erase and rewrite phase meddle with proper development of cloned embryos.

"The new imprinting mechanism may eventually offer a target for treating such developmental failures," Zhang says.

More information: Azusa Inoue et al, Maternal H3K27me3 controls DNA methylation-independent imprinting, *Nature* (2017). DOI: 10.1038/nature23262

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