Tet1 protein helps developing germ cells wipe genes clean of past imprints

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A protein called Tet1 is partly responsible for giving primordial germ cells a clean epigenetic slate before developing into sperm and egg cells, according to a new study by researchers at Boston Children's Hospital. This discovery could help provide clues to the cause of some kinds of neonatal growth defects and may also help advance the development of stem cell models of disease.

The findings were reported online Dec. 1 in *Nature* by a research team led by Yi Zhang, PhD, and Shinpei Yamaguchi, PhD, of Boston Children's Program in Cellular and Molecular Medicine.

Each of our cells carries two copies, or alleles, of every gene in our genome, one from each parent. In certain genes, one allele is imprinted—marked with small chemical tags called methyl groups—to keep it silent and prevent biological conflicts from arising between the two copies.

Before they mature into sperm or egg cells, primordial germ cells' imprinting patterns are erased and then re-established in an allele-specific manner. This process ensures that in the developing embryo only one member of each pair of alleles is expressed.

Zhang and Yamaguchi showed in a mouse model lacking the Tet1 gene that loss of the Tet1 protein prevented primordial germ cells from erasing their imprints, leading to embryonic lethality and reductions in the size of live-born offspring. The results suggest that Tet1 mutations

may contribute to certain human birth defects and also provide insight into the mechanisms underlying the erasure process.

"We've long known what proteins are responsible for establishing imprinting patterns," says Zhang. "How erasure occurs has been less clear.

"We realize that Tet1 does not act alone in the erasure of genomic imprints, but is one important factor," he added. "We need to do additional work to understand what other proteins are involved."

Zhang noted that proper imprinting also has a role in cellular reprogramming, such as the generation of induced pluripotent stem (iPS) cells.

"Proper imprinting pattern is critical for the maintenance of normal development and differentiation, but abnormal imprinting pattern is frequently observed in iPS cells after reprogramming," he explained. "Understanding how imprints are erased could lead to more effective methods of high-quality iPS cell generation."

Provided by Children's Hospital Boston