NOTES FROM MOM

DNA'S MARGINALIA | BY LEAH KAUFFMAN

When just about two days old, a mammal's embryo is only eight cells large. Although at this early stage it's impossible to tell what part of the developing embryo one of those eight cells might become—a giraffe's leg or a human's brain—they're getting important instructions that will determine their fate: The DNA they contain is undergoing genomic imprinting, a process that places molecular marks on our DNA. The work of J. Richard Chaillet, a University of Pittsburgh researcher and scientific director of Pitt's new Transgenic and Chimeric Mouse Facility, suggests that these chemical marks greatly impact the survival and health of the fetus to be—even though they are made days before the embryo implants in the uterus and well before critical organs and systems start to form.

The marks that Chaillet studies don't make up the genetic code itself, but chemical additions to it—like notes in the margin of a book—that are passed along as the DNA replicates.

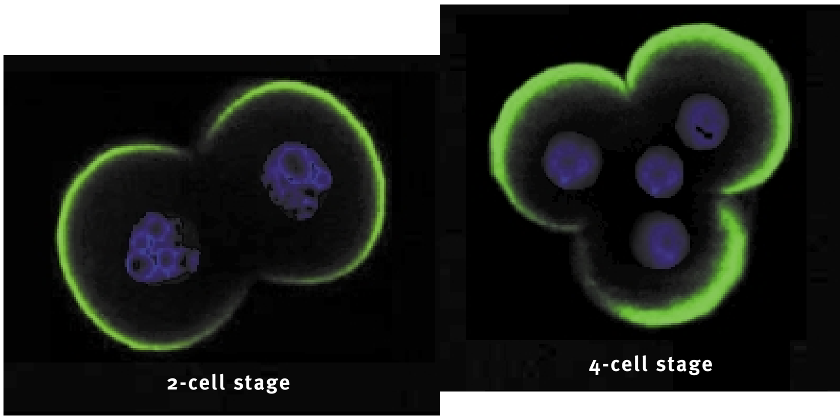
These genomic notes usually serve to shut off expression of the genes they mark, but it's not yet clear why. Geneticists do know we each have the same notes on the same parts of our genomes, and that most of the notes are first written on the DNA of the unfertilized egg and inherited from our mother. Only a few notes (genomic imprints) are inscribed first on the sperm's DNA. Most imprints are passed along the maternal line to offspring, where they continue to mark the embryo's genetic material from the earliest moments of development.

To understand how an embryo gets its genomic notes from its mother, Chaillet, an associate professor of pediatrics and human genetics, and colleagues created a line of mice without a gene that makes a protein known to play a part in imprinting called Dnmt1o (a methylating protein that female mice usually develop very early on). When Chaillet's Dnmt1o-free females were mated, they conceived but produced almost no live births. Most of the fetuses died during the last third of gestation.

Chaillet traced these deaths back to a failure to take notes, at the molecular level, that is.

His experiments showed that imprinting—the chemical marginalia step in DNA's editorial process—was not taking place as the embryos' eight cells divided into 16: Only about half of the DNA in embryos without Dnmt1o had been annotated. Chaillet concluded that Dnmt1o is responsible for jotting notes on DNA as it replicates and rearranges into new double helices during that one, short stage of development. Because all of the organs and tissues of the embryo eventually result from the further division of just those few cells, this single small error in note taking has devastating results. But not immediately. It takes some time—many, many cell divisions—for enough nonimprinted cells to accumulate and compromise fetal development. Chaillet suspects that imprinting blanks such as these might explain some mysterious deaths of human fetuses in late gestation and of infants just after birth.

In normal mice, the Dnmt1o protein is made when the mouse mom herself is just an embryo, when her own eggs are developing.



With just one more cell division, the protein (green) will make its way from the cytoplasm into the nuclei (blue) to do the crucial job of imprinting DNA. Chaillet has shown this very early developmental step helps ensure that the embryo grows normally.

The protein is stored outside the nucleus of the cell in the cytoplasm until after the egg is fertilized, then it goes to work directing imprinting in the embryo. The Dnmt1o journey from mother to offspring is an example of a larger phenomenon called maternal effect, the notion that the embryo's development is directed by substances made by the mother's DNA (like Dnmt1o) rather than by the embryo's own.

Maternal effect is known to be a factor in the development of some lower organisms. In fact, Christiane Nüsslein-Volhard and Eric Wieschaus earned a Nobel prize for, in part, their work on maternal effect in fruit flies. Chaillet and his team are one of the first to demonstrate it in mammals. ■

FOR MORE INFORMATION:
On Chaillet's recent breakthrough:
http://www.cell.com/content/vol104/issue6
On the Transgenic and Chimeric Facility:
http://www.genetics.pitt.edu/tcmf/