

JUNE 14, 2009

Sperm's Genes Packaged with Instructions for Development

New research shows that a father's sperm passes along a previously unrecognized set of instructions that helps guide the early development of his children. The instructions likely tell the developing embryo when specific genes should be turned on or off.

Scientists have found that in sperm, most paternal genes important for embryonic development are flagged with special proteins bearing chemical tags. These proteins and their tags, called modified histones, influence when developmental genes and other key processes are turned on, shut off, or put on hold at critical stages in an embryo's growth.

The findings were reported in an advance online publication on June 14, 2009, in the journal *Nature*.

"You need to make sure those genes from the father turn on for normal development. . .and they have to turn on at the right time."

- **Bradley R. Cairns**

During fertilization, sperm and egg combine to form a zygote, a single cell that later divides to become many cells, and many cell types. Each cell type must emerge at the right time, and in the right place, for a healthy embryo to develop. The new research by Howard Hughes Medical Institute investigator Bradley R. Cairns addresses how an organism's genetic material is packaged to execute that carefully choreographed process.

The findings show that sperm genes are packaged along with chemical "guideposts" that help determine which genes should be turned on or off at specific stages of development, says Cairns, who collaborated with Douglas Carrell and other colleagues at the University of Utah. Those developmental guideposts are epigenetic—meaning they regulate gene access and utilization without changing the DNA sequence of a gene.

Epigenetics influences gene expression in several ways: One is through methylation—the addition of a methyl group to a DNA molecule to deactivate a gene. Demethylation—subtraction of a methyl group—activates the gene. Genes can also be silenced or activated by modifying histone proteins that serve as spools on which DNA strands are wrapped.

Previous work in Cairns' lab, in zebrafish and yeast, had shown that histones can package certain genes so they remain flexible during development. His group showed that genes in the 'off' position can also be poised to turn on later. "It's gene packaging," he says "that determines the potential for a gene's activity."

However, about 96 percent of the histone proteins in the genome are eliminated as sperm mature. The race to fertilize an egg goes to the swift—and having a small head, with DNA packaged even more tightly, is advantageous. So the histones in mature sperm are largely exchanged for another protein, protamine, which further compacts the DNA.

Many scientists have reasoned this protein swap might limit how much information is transmitted from sperm to egg during fertilization. But Cairns says the new work suggests that isn't true. Using sperm from fertile human donors, the researchers separated out the chromatin, which contains the genetic material and proteins that make up chromosomes, into histone-bound and protamine-bound fractions. Their analyses of both fractions revealed that histones, although comparatively small in number, were still maintained at hundreds of genes important for embryo development.

"Those genes are the important decision makers in the embryo," Cairns says. "You need to make sure those genes from the father turn on for normal development ... and they have to turn on at the right time."

The sperm apparently marks the genes that turn on early in embryo development with specific types of modified histones, Cairns says. A different type of modification is placed on genes that turn on later—a sort of "do not open till Christmas" label. This tagging ensures that genes are activated only when the embryo is ready for them—such as to achieve differentiation into cell types that constitute different body tissues.

Cairns explains that under this scheme, some genes that are activated early in development, for example, are marked with a "green light" indicating they should be turned on. Others have both a green light and a red light, and require the removal of the red light to turn on later in development.

To transmit its information and guide development, this labeling must remain intact upon fertilization, when the protamine releases from the paternal DNA and the remainder of the sperm genome is repackaged with the egg's histones.

This packaging parallels the way in which developmental genes are packed up in embryonic stem cells, Cairns says, with genes poised to act by the mix of green- and red-light markings. Such packaging could explain transgenerational inheritance, the proposition that traits can be passed to offspring by biochemical means other than DNA sequence. As for how a mother's genes receive their instructions for development, "eggs remain a mystery," he says. "This is an issue we are now addressing in zebrafish, from which thousands of eggs are easily obtained."

Cairns says he is awestruck by nature's solution to the problem of how to keep all genes from being transcribed at once—which would be disastrous—or of packaging them so tightly that the DNA can't be accessed. "What has evolved is this very sophisticated and beautiful system of tailoring gene packaging and modifying gene packaging to allow for regulated access to the genes."