

Does dad's diet determine a baby's genetic fate?

BY GEOFFREY MOHAN (ADAPTED FROM THE LA TIMES, DECEMBER 11, 2013)

Men may want to have a healthier diet in the months before procreation. A recent study suggests a father's vitamin B9 (folate) deficiency may contribute to birth defects in offspring. The study, published online Tuesday in the journal *Nature*, shows that a male mouse's diet can affect the signaling of genes contained in its sperm. As a result, those fathers apparently pass along an "environmental memory" that affects how the genetic code is expressed for the baby both in the womb and during a lifetime.

The study adds to a growing pile of evidence suggesting that characteristics outside of the genetic code may also be acquired from our parents through "epigenetic" inheritance. Epigenetics studies how some molecules act as DNA markers that change how the genome is read and expressed. We pick up these epigenetic markers during our lives and in various locations on our body as we develop and interact with our environment.

Attention to diet, particularly folate, has been an important focus of women's reproductive health. But until recently, the male's contribution to an offspring's epigenetics has attracted far less attention. "It's always put on the mother that it's her health that determines the health of the baby," said McGill University biologist Sarah Kimmins, an author of the study. "But our research shows that guys also need to consider their health, and what they're eating and what they're doing, in terms of the future health of their offspring."

Using mice as a model, researchers related low folate levels in dad to changes in gene expression of several dozen genes in offspring. These include genes involved in development of the central nervous system, and in some diseases such as cancer and diabetes.

In particular, epigenetics researchers have focused on the exchange of a carbon atom bonded with three atoms of hydrogen — a methyl group — among certain base pairs of DNA and the histone proteins that package and shape them. "If you don't have enough folate, you don't have enough of these methyl groups, and these methyl groups act like tags on the DNA, to tell genes whether they should be really strongly on, on just a little bit or off," said Kimmins, who holds the Canada research chair for epidemiology, reproduction and development. "So if you don't have enough of those biochemical flags, you're going to transmit that to the embryo via the sperm."

Methylation lies at the heart of the deprogramming and reprogramming that goes on when sperm and egg meet and begin the process of cell division and specialization. It facilitates the development of complex human biology, but sometimes opens paths that lead to cancer and disease.

Studies have shown that epigenetic changes affect not only the individual during a lifetime, but her progeny. One study showed that genetic signals persisted in the twin offspring of women exposed to the Nazi-imposed food embargo of the Netherlands in 1944-1945, for example. Another suggested that high prenatal exposure to toxic

chemicals in utero could lead to inherited genetic changes two generations later.

On the paternal side, a 2010 study in the journal *Nature* showed that a high-fat diet among male mice affected expression of an array of genes in daughters, including those regulating insulin storage and release. Another study of mice published in the journal *Cell* that same year showed that a father's low-protein diet altered the fat-regulating genes of offspring.

Researchers theorize that epigenetic signaling is a widely conserved evolutionary trait that can safeguard a species' genetic code and propel cellular-level adaptation to a changing environment.

But today's environment sends signals that are at best mixed — through exposures to toxic chemicals, and consumption of foods high in fat and low in vital nutrients. The consequences, medical experts say, are rising rates of cancer, birth defects, heart disease and diabetes.

The folate deprivation regime of the mice in the current study was meant to mimic food scarcity already experienced in many regions of the world, Kimmins noted. But it also paralleled poor folate processing typical in obesity, which is rising in areas of relative food abundance.

The correlations found in the study don't identify the "smoking gun" mechanism that connects paternal diet and defects in offspring, but offer promising leads for additional research. A good part of the problem is technical, Kimmins noted — it is hard to isolate cells in early developmental stages, and the rapid process of cell division makes it difficult to capture biochemical changes that can be multi-factorial and time sensitive.

"No, we can't say we can directly track the mechanism, but we can certainly say it's the first time we've documented that food changed the sperm epigenome, which then was linked with developmental genes, and with birth defects," Kimmins said.

Others not involved in the study called the correlations intriguing.

The study "drew out some biologically plausible genes that are critical in processes that we think are important in human development and also in long-term outcomes" of health, said Jane Figueiredo, an epidemiologist at USC's Keck School of Medicine who has researched epigenetic factors in disease. "Certainly folate is not going to be the only contributor to different methylation patterns, but it's a key finding that at least it's contributing."

James Crott, who studies human nutrition and aging at Tufts University, said such studies will have to be replicated with larger samples. His research has shown similar epigenetic effects of B-vitamin deficiency on colorectal cancer genesis in mouse offspring.

"There's a lot to be done in this field, but this is an important contribution," he said.