

Medical News & Perspectives

The Paternal Epigenome Makes Its Mark

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For decades, prenatal advice has mainly focused on mothers. Leading up to and during pregnancy, women are told to take folic acid supplements, stop drinking and smoking, avoid high-mercury fish, and maintain healthful weight gain, among other wisdom. That advice is prescribed by physicians and public health experts to promote healthy pregnancies, normal fetal development, and long-term offspring health. A father's behavior can also influence the health of a pregnancy, by exposing his partner to secondhand smoke or domestic violence, for example. But there's a growing belief among scientists that a man's behaviors and environmental exposures may also shape his descendants' development and future health *before* sperm meets egg.

Researchers now understand that sperm contains a memory of a male's life experiences, ranging from his nutritional status to his exposure to toxic chemicals, said Michael Skinner, PhD, a professor in the school of biological sciences at Washington State University. This information is captured in alterations to the epigenome, the suite of molecular on-off switches that regulate gene expression.

Moreover, it's now been well-established through animal studies that some "epimutations" are heritable. Skinner and others, for example, have provided evidence in rodents that male exposure to endocrine disruptors and other environmental toxicants can induce epigenetic changes in sperm, which in descendants can cause infertility and other diseases.

Epigenetic information can be embedded in sperm in the form of changes in DNA methylation—the addition of chemical "tags" that switch genes "on" or "off"—or histone modifications—chemical tags on histone proteins, which regulate how DNA is condensed. In addition to these epigenetic marks, researchers also have become increasingly interested in changes in noncoding RNAs, such as microRNAs (miRNAs), which are involved in gene silencing and can be present in sperm.

Last year, a review of human and animal research suggested that epigenetic

changes may be the underlying mechanism by which paternal factors such as age, diet, weight, stress, and alcohol consumption contribute to a range of health outcomes in offspring including birth defects, behavioral problems, developmental disorders, obesity, diabetes, cardiovascular disease, and cancer.

The senior author of the review, Joanna B. Kitlinska, PhD, an associate professor in the department of biochemistry and molecular and cellular biology at Georgetown University, cautioned, however, that all of the associations between paternal epimutations and offspring health in humans are still just that—associations. "There really is no direct proof at the moment," she said.

Providing direct evidence that heritable environmentally induced epigenetic changes in human sperm (or eggs) increase susceptibility to disease in later generations remains challenging. But the epidemiological hints and laboratory evidence are starting to coalesce into a relatively simple public health message: When it comes to preconception health, fathers matter too.

From Men to Mice

A series of studies of historic cohorts from Överkalix in northern Sweden published last decade suggested that information about life experiences could be passed down several generations through the

male line and could influence descendants' health. In 2001 Lars Olov Bygren and coinvestigators from Umeå University in Sweden demonstrated that men born in 1905 who experienced food scarcity before puberty—when primordial sperm cells are developing into mature sperm—had paternal grandchildren with a lower relative risk of early death. The reverse was true for men who had plenty to eat: Their sons' children were more likely to die young.

The researchers teamed up with a group in the United Kingdom to publish a larger study in 2006 that additionally included Överkalix cohorts born in 1890 and 1920 and looked at sex-specific effects. This study revealed that the food supply of paternal grandfathers was only linked to their grandsons' mortality rate, while the food supply of paternal grandmothers was only linked to their granddaughters' mortality.

Marcus E. Pembrey, MD, coauthor of the 2006 article and an emeritus professor of pediatric genetics at University College London, explained in an email, "The sex-specific effects were difficult to put down to 'cultural' inheritance," adding that "the Överkalix data demonstrate some molecular 'memory' of the ancestral exposure."

When the collaboration began, Pembrey was director of genetics on the landmark Avon Longitudinal Study of Parents and



Children (ALSPAC) at the University of Bristol. In the 2006 article, he and his co-authors also presented data from a cohort of fathers in the ALSPAC study. In this group, men who took up smoking before puberty had 9-year-old sons with higher BMIs than men who first lit up later in life, suggesting that the timing of the ancestral exposure matters. A [follow-up study](#) published in 2014 found that the sons of early smokers—who themselves were not necessarily overweight—had an average of 5 to 10 kg more body fat in their teens than their peers.

Several other epidemiological associations between a father's health prior to conceiving and the health of his children have emerged. For example, there are also some [indications](#) that a father's drinking may contribute to fetal alcohol syndrome-like symptoms, specifically low birth weight, congenital heart defects, and mild cognitive impairments.

Experiments in animals suggest that epigenetic changes in sperm may explain some of these associations. Male rats [administered alcohol](#) for 9 weeks prior to breeding, for example, have epimutations in their sperm, which may account for the significant decrease in fetal weight of their offspring. Many other [studies](#) have found a range of physiological and behavioral abnormalities in offspring, including altered organ weights, decreased grooming, and increased anxiety-like and impulsivity-like behaviors, in rodents whose fathers—but not mothers—were given alcohol, with sperm epimutations being the presumed underlying mechanism.

Early this decade, a spate of [animal studies demonstrated](#) that, in addition to toxins and alcohol, paternal weight and eating patterns—such as high-fat or low-protein diets—also appear to alter the sperm epigenome and offspring health. In one mouse [study](#), a paternal diet low in folate was associated with an increase in birth defects in offspring compared with a paternal diet sufficient in folate. The fathers who consumed less folate had abnormal methylation of genes implicated in development and chronic disease such as diabetes and cancer.

And just last year, [German researchers found](#) that male or female mice with diet-induced obesity produced daughters (but not sons) who were more likely to be obese than those whose parents were both

lean. Critically, the offspring were created through in vitro fertilization and gestated by lean surrogate females, eliminating potential confounding by gestational environment and pointing the finger squarely at epigenetic alterations.

Studies published last year also suggest a link between paternal [dietary patterns](#) or diet-induced weight gain and increased birth weight and breast cancer risk in female offspring. [One of these studies](#) identified shared epigenetic changes present in both the sperm of overweight male mice and the breast tissue of their female offspring. These alterations included reduced expression of miRNAs that regulate insulin receptor signaling, among several other well-characterized signaling pathways known to play a role in tumorigenesis. Alterations in miRNA expression may therefore underlie the metabolic reprogramming that, in turn, increases breast cancer risk.

"We see that the daughters of overweight fathers have increased breast cancer risks the same way as daughters of mothers who are overweight in pregnancy also have increased breast cancer risks," said Sonia de Assis, PhD, the study's senior author and an assistant professor of oncology at Georgetown University Medical Center. "I think we've been looking at only the half of the problem."

Humans: The Next Frontier

Researchers are just beginning to tease out these underlying epigenetic mechanisms in humans. Investigators on the Newborn Epigenetics Study (NEST) at Duke University provided the first molecular evidence in [2013](#) and [2015](#) that a man's lifestyle may be imprinted on his child's epigenome.

The researchers, including Adelheid Soubry, PhD, head of the epidemiology research center in the department of public health and primary care at the Catholic University Leuven in Belgium, discovered altered epigenetic marks on genes associated with embryonic growth, as well as metabolic disorders and cancer in later life, in the cord blood of newborn infants whose fathers were obese. These marks were independent of maternal obesity and different in infants of nonobese fathers.

Human sperm itself also tells a similar tale. Last year, Soubry [found](#) epimutations on a number of growth-regulating genes in the sperm of obese and overweight men. Moreover, some of the epimutations in

sperm were similar to those previously identified in the cord blood of infants of obese fathers, suggesting they may be passed on from father to offspring. Research in larger study populations will be needed to confirm this, Soubry said.

And it's not just a father's weight that can change his sperm epigenome. In February, Skinner published [findings](#) showing that men who underwent chemotherapy for bone cancer in their teens shared a signature of epimutations in their sperm about a decade later. Although his sample size was small—18 cases and the same number of controls—Skinner said the persistence of changes suggests that toxicants may permanently alter epigenetic marks in sperm stem cells, resulting in a lifetime of epigenetically altered sperm.

Skinner wants to see more studies on human paternal exposures and impacts on offspring and subsequent generations. He emphasized that studies should probe molecular-level changes in the epigenome that may explain the associations. He and a coinvestigator plan to study health outcomes in the offspring of human and rodent chemotherapy recipients. "When you do the exposure and you change the epigenetics of the germ line, you can't predict what's going to happen," he said. "You just sort of have to look and see."

It's not fully understood how epigenetic changes may persist through generations. Two rounds of near-complete epigenetic erasure and reprogramming occur between fertilization and implantation and during gonadal sex determination. How some epimutations appear to survive these waves of reprogramming to promote epigenetic transgenerational inheritance will be an important question for future research.

Malleable Marks

There are early indications that some paternal lifestyle-associated effects on sperm and offspring can be reversed, with [exercise and dietary changes](#) or [surgery-induced weight loss](#), for example. Although several windows of susceptibility may exist for paternal exposures and some changes in sperm may be permanent, the few months leading up to conception may not be too late to make lifestyle changes, Soubry said. de Assis agreed: "If they can't do it for their entire life, then at least in that period before conception."

Soubry suggested that physicians can encourage male patients who plan on conceiving to eat a nutritious diet, quit smoking (even temporarily), drink moderately, and manage stress—all of which the Centers for Disease Control and Prevention already [recommends](#) for fathers-to-be. "That advice cannot harm, and I think it

can even help to reduce the risks later on for the child," Soubry said. Of course, behavior matters *during* pregnancy, too. Fathers—along with mothers and domestic partners—can have a profound effect on the health of pregnancies.

Kitlinska stressed that future studies should look at the combined effects

of maternal and paternal factors, including epimutations. "Usually when we design experiments, we look at the effect of paternal exposures or maternal exposures, but really I think it's an interplay of both." ■

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