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Heritable Epigenetics

Study validates that chemical exposures in the womb can trigger changes in gene expression

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A study on four classes of chemicals—plastics, pesticides, dioxins, and hydrocarbons—has confirmed that exposure of a fetus to man-made chemicals in the womb can result in heritable changes in gene expression, even to offspring generations later that were not directly exposed to the chemicals (*PLoS One,* DOI: 10.1371/journal.pone.0031901).

The work is the latest from the lab of Michael K. Skinner of Washington State University, Pullman. Skinner's research is helping change preconceptions in the field of epigenetics, which is the study of the still-mysterious biochemical processes that switch genes on and off. Scientists believe that understanding epigenetic changes holds the key to understanding the mechanisms of disease.

Epigenetic marks such as methylation of cytosine bases in DNA leave a permanent lifetime imprint without mutating the underlying DNA sequence. These marks were initially thought to be transient and erased in germ-line cells, which develop into eggs and sperm, and therefore not passed on to subsequent generations.

But in a 2005 paper in *Science,* Skinner's lab reported the first experimental evidence that chemical exposures can cause permanent epigenetic changes in the germ line (DOI: 10.1126/science.1108190). They exposed pregnant female rats to the fungicide vinclozolin and the insecticide methoxychlor and found that 90% of the male offspring after three generations still exhibited a decrease in fertility. Because military personnel are regularly exposed to an array of chemicals in their work environments, Skinner's research attracted the attention of the Department of Defense, which prompted the new study.

"DOD asked us to test sets of chemicals with our protocol to see if there is any chance that certain chemical exposures could promote epigenetic transgenerational inheritance of disease in people," Skinner explains. DOD's primary concern is drinking water, which can contain bisphenol A and phthalates that leach from plastic containers. Other concerns are the insecticide permethrin and insect repellant *N,N*-diethyl-*m*-toluamide (DEET); dioxins, which are chlorinated compounds that are released into the environment when burning trash; and jet fuel, a mixture of C_3 to C_{20} hydrocarbons that the military often sprays on the ground to control dust.

Skinner's team injected pregnant rats with high, but nonlethal, doses of the four sets of chemicals. They used an abnormal route of exposure and doses well above normal environmental exposure amounts, Skinner points out, because his group was trying to induce the epigenetic phenomenon.

The researchers found consistent sets of epigenetic marks in the next three generations of rats, none of which were exposed to the chemicals. Furthermore, in the female offspring they observed earlier than normal puberty and fewer ovarian follicles, which later become eggs. In the male offspring they found increased decay and death rates of sperm cells, similar to the findings in the *Science* study.

"It's not surprising that you can treat pregnant female rats with an endocrine disrupter and see defects resulting from epigenetic problems in the offspring," notes epigenetics expert John R. McCarrey of the University of Texas, San Antonio. "The big surprise in the results from Skinner's original paper—the new study is an important validation of those results—is that the epigenetic changes persist in subsequent generations.

"That's what's scary," McCarrey continues. "It means that something your great-grandmother was exposed to could impact you and your children or grandchildren."

Skinner says he didn't expect all the chemical mixtures to work, but they did. "That tells me it doesn't matter so much what the signaling mechanism is," Skinner says, "but that a large number of chemicals have the capacity to trigger heritable epigenetic changes during a critical window of fetal development."

In addition, each of the chemical mixtures promoted a different DNA methylation pattern in the sperm, Skinner says. That means there are exposure-specific epigenetic biomarkers. “In the future, that might give us a way to analyze an individual’s epigenome and accurately predict adult-onset diseases or the possibility of passing on inheritable diseases to children,” Skinner suggests. “That concept is something we definitely didn’t expect when we began this study.”

With a better mechanistic understanding, scientists might figure out how to remove epigenetic marks from where they normally exist or create them where they normally don’t exist, McCarrey says. “For someone like me who is a basic researcher, it’s very exciting. We have a lot to learn.”

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