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November 30, 2007

Mom's Duties Begin Very, Very Early

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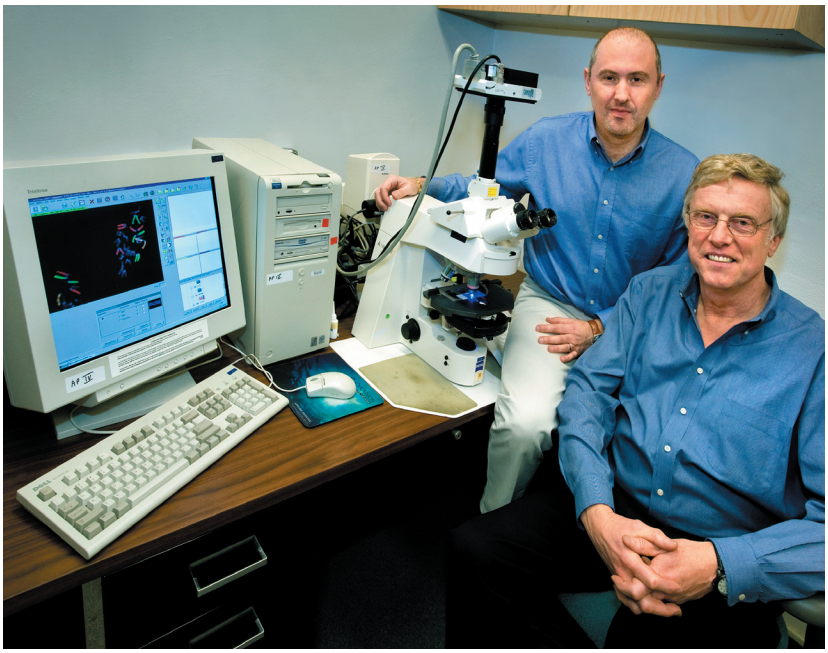
A mother's work is never done, but who knew it started this early? Long before mom applies band-aids to scraped knees, she's tasked with repairing DNA breaks, in the fertilized egg, which were passed on by dad. Now, Berkeley Lab scientists have pinpointed the genes that regulate this first foray into motherly care.

"We've identified the maternal genes responsible for repairing DNA damage in the fertilized egg that were transmitted by sperm," says Francesco Marchetti of the Life Sciences Division.

This urgent bit of maternal DNA repair, which in humans occurs during the first several cell-division cycles after fertilization, is critical to preventing chromosomal problems in the fertilized egg, also called a zygote, which can lead to pregnancy loss, infant mortality, birth defects, and genetic diseases in offspring. Scientists have long known that the maternal genotype is equipped to fix double-strand breaks in the DNA donated by dad. But they didn't know which genes regulate this all-important work.



Francesco Marchetti (left) and Andy Wyrobek studied the effects on DNA repair in fertilized eggs in mice when chromosomes from the males were damaged and the females lacked specific genes.

To explore this question, Marchetti and fellow Life Sciences Division senior scientist Andy Wyrobek, working with scientists from the Netherlands, turned to mice. First, they exposed male mice to ionizing radiation, which induces double-strand breaks in the DNA in their developing sperm. During the final two weeks of sperm development in mice—and during the final three weeks in humans—DNA within sperm lacks the ability to repair itself.

"This means that damage that is sustained during this window is most likely transmitted to the egg, and then it's up to the egg to repair it," says Wyrobek.

Seven days after irradiating the male mice, the scientists mated them with three types of female mice. One type of mouse lacked a gene called *scid*, which repairs DNA double-strand breaks. Another mouse lacked a gene called *Rad54*, which ensures that the genetic information in the damaged DNA remains intact. A third type of mouse was normal and had both genes, and was used as a control. What they found surprised them.

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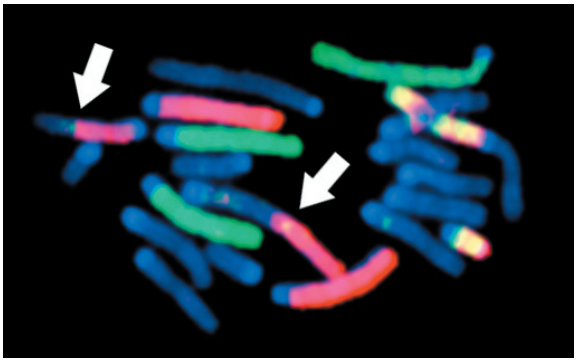
"When we removed the *scid* gene, which is the gene needed to repair double-strand breaks, the frequency of zygotes with chromosomal aberrations doubled," says Marchetti.

In addition, female mice missing the *Rad54* missing gene also had an increase in aberrations in their fertilized eggs, but these were confined to a smaller subset of genetic problems. Overall, the *scid* gene played the largest role in fixing dad's DNA.



Female mice lacking the* scid *gene are unable to efficiently repair double-strand breaks (arrows) in chromosomes of the zygote which originated in the sperm of irradiated male mice.

"The ability to repair DNA double-strand breaks is critical to fixing the damage introduced by sperm, and for the first time we've linked this repair mechanism to a specific gene," says Wyrobek. "This means that if an egg that is able to repair double-strand breaks in DNA, then it can repair the damage transmitted by sperm. But take away this mechanism, and 50 percent of this damage gets through, which increases the risk of pregnancy loss or of a child being born with a chromosomal defect."

Although their work focused on mom's handiwork in cleaning up dad's DNA, it doesn't let dad off the hook. According to Marchetti, there are steps that dads can take to ensure that mom doesn't have to work overtime to repair his DNA. Chief among them is to stop smoking, which is known to cause DNA lesions.

Their research may also help in vitro fertilization efforts, which currently focuses on ensuring that an embryo develops in an optimum environment. Now, it's clear that the genetic health of the zygote during its earliest stages is as important as a developing embryo's surroundings.

The data collection phase of Marchetti and Wyrobek's work was conducted while the two were at Lawrence Livermore National Lab, while the data analysis phase of the research was conducted after the scientists moved to Berkeley Lab.

Additional information

"Disruption of maternal DNA repair increases sperm-derived chromosomal aberrations," by F. Marchetti, J. Essers, R. Kanaar, and A. J. Wyrobek, appears in the November 6, 2007 issue of *Proceedings of the National Academy of Sciences* and is available online to subscribers at http://www.pnas.org/cgi/doi/10.1073/pnas.0705257104.

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