Serendipity reveals sex bias in embryo development

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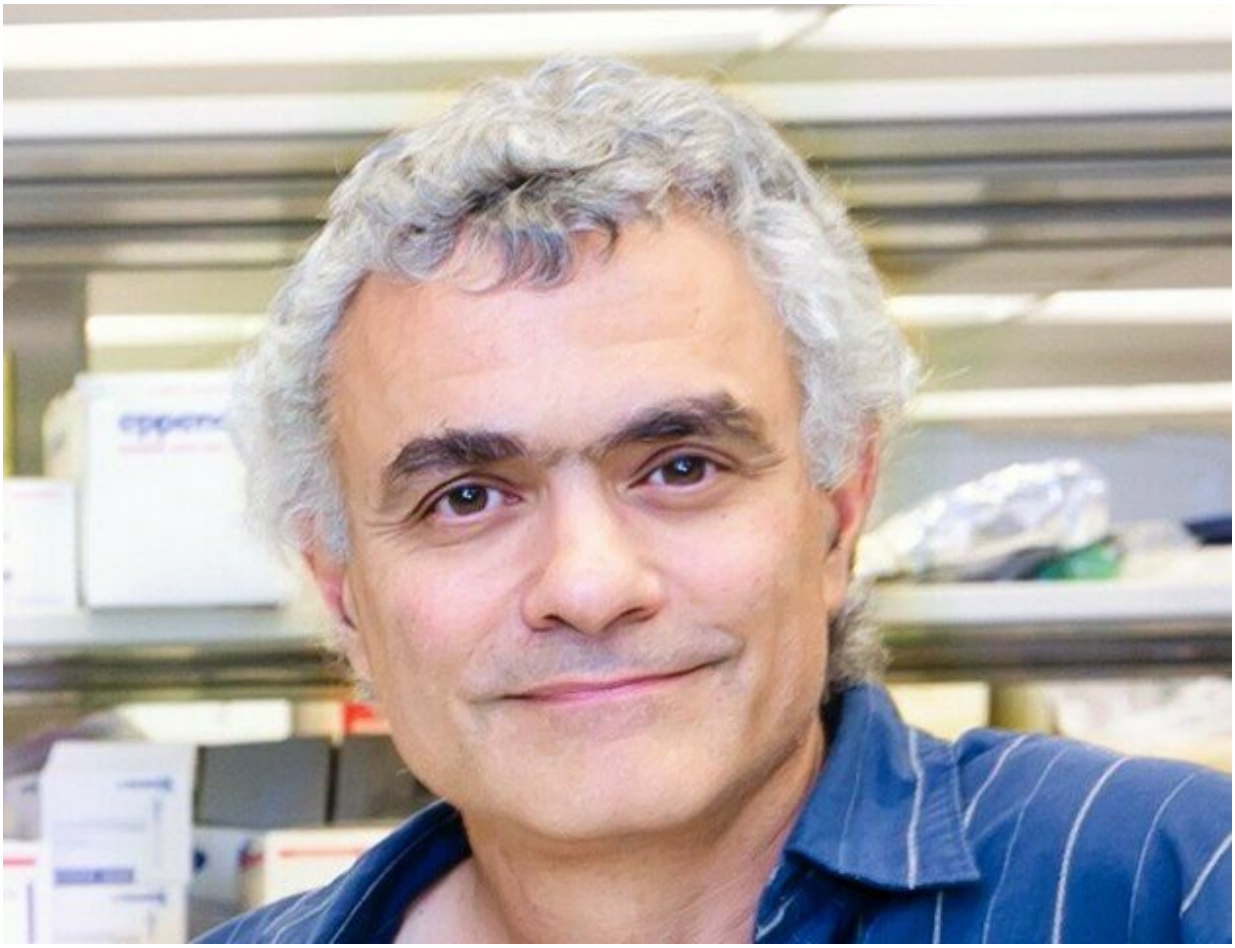

John Schimenti. Credit: Cornell University

New published research from the College of Veterinary Medicine shows

that heightened levels of genomic instability can prove fatal to female embryos in mice.

In the paper, senior author and professor of genetics John Schimenti found that when DNA is damaged during its embryonic replication process, the inflammation response from the cell is much more likely to be lethal to female embryos, which do not have the intrinsic protection of testosterone that male embryos have.

"We ruled out other potential factors," said Schimenti. "It was the anti-inflammatory effects of exogenous or endogenous testosterone that protected the male embryos." When researchers applied testosterone and other anti-inflammatories like ibuprofen to female embryos, they survived the inflammation response.

The paper, "Female-Biased Embryonic Death From Inflammation Induced by Genomic Instability," published Feb. 20 in *Nature*. Postdoctoral research associate Adrian McNairn and Chen-Hua Chuang, Ph.D. '11, are co-lead authors.

The Schimenti lab initially set out to discover mutations in genes that caused elevated genomic instability, with the ultimate purpose of identifying new tumor suppressors. They indeed isolated mouse strains with phenotypes of cancer susceptibility due to DNA repair or replication defects, both of which cause genomic instability. The lab also found mice with infertility due to defects in meiosis or germ cell development.

While working with one of the strains that possess a cancer-causing DNA mutation, McNairn and Chuang noticed that they produced more male than female mutant offspring. They pursued that thread of inquiry for this paper. Schimenti described it as an unexpected development. "It shows that serendipity still plays a major role in science," he said.

This research illustrates the importance of increasing recognition that males and females do not have identical biology. "If you ignore sex in a study of any sort, you're not getting the full story," said Schimenti.

Embryonic development is a period of rapid cellular proliferation. As an embryonic cell grows, it must replicate its DNA and make copies of all the chromosomes, amounting to approximately 3 billion building blocks.

If there are more defects than normal in that process – if the genome is unstable – a hunk of nuclear DNA can end up in the cytoplasm of the cell. The cell interprets this as a foreign threat and mounts an inflammation response, proving lethal to female embryos in the process.

Scientists have researched genomic instability in cell culture and cancer studies because of its connection to tumor initiation and growth. Whereas most of that work is performed at a basic level to understand its fundamental mechanisms, it was Schimenti's research in whole animals that led to this discovery.

"Working in a whole animal is a different story from working with cells in a petri dish," said Schimenti. "It's much more complicated but reflects the complex impact of animal physiology."

Schimenti thinks their findings will cause researchers to examine past records in which they've dealt with similar mutations to account for the sex bias.

"In future work, we'd like to examine exactly why these female embryos are dying, the cells tissues that are culpable and to ultimately find if this is happening in humans as well," he said.

More information: Adrian J. McNairn et al. Female-biased embryonic death from inflammation induced by genomic instability, *Nature* (2019).

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