The Nature Institute

Unintended Effects of Genetic Manipulation
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Posted: January, 2019

New Studies Fail to End Controversy about How to Interpret Last Year's Surprise Results in U.S. Human Embryo Research

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The journal *Nature* has published a set of contrasting new papers that attempt to shed light on the controversy about how to interpret the surprise results of a major 2017 study that was attempting to genetically engineer human embryos in the lab to correct a genetic mutation associated with heart disease. (The Nature Institute's earlier report on that research and the controversy it sparked is available here.)

The team responsible for the original research, led by Shoukhrat Mitalipov of the Oregon Health & Science University, announced last year that they had succeeded in using CRISPR-Cas9, a powerful new biotechnology tool, to correct a disease-related version of a gene from the paternal side in human embryos at the very earliest stages of development. But they reported that the correction they believed they detected in many of the embryos occurred in a surprising way – not how they had intended. The embryos appeared to have used the normal maternal version of the gene as the template to repair the site where CRISPR-Cas9 had cut out the abnormal paternal version of the gene, rather than incorporating the template of synthetic DNA researchers had inserted.

Other researchers, however, argued that such a process was highly unlikely. What was more probable, some suggested, was that the cellular response to the cut made with CRISPR-Cas9 generated large deletions and that the methods Mitalipov's team used to make sure the abnormal version was corrected may not have been detailed enough to reveal how much was deleted. So the team may have failed to detect that there was no paternal version of the gene at all — that only the maternal version may have been present.

The package of follow-up studies in the Aug. 9 issue of *Nature* include the peer-reviewed version of a critique that first aired last year, soon after the original research was published. The package also includes a new study conducted by Australian researchers. In using CRISPR-Cas9 with very early stage mouse embryos, they found that relatively large, unintended deletions of genetic material were frequently generated of the sort that could have fooled Mitalipov's team.

The same issue of the journal also contains a reply from Mitalipov and his colleagues. It includes detailed new genetic analyses related to their initial sample and reference to new, not yet peer-reviewed research by others with mice — all of which, they argue, strongly support their original conclusion. But reports in major science publications indicate that at least some of their most outspoken critics are still skeptical and believe that additional studies are needed to fully clarify the issue. On one point, however, it appears that all involved agree — what the Mitalipov reply referred to as the need for better understanding of "the complex nature of DNA repair."

Sources

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