Unintended Effects of Genetic Manipulation
A Project of The Nature Institute
Project Director: Craig Holdrege
Email: nontarget@natureinstitute.org

20 May Hill Road • Ghent, NY 12075 USA • Tel: (518) 672-0116 • http://natureinstitute.org

Posted: January, 2019

CRISPR-Cas9, Popular New GMO Tool, Can Cause Extensive Genomic Damage, British Researchers Report

Colleen Cordes

Experimental use of CRISPR-Cas9, the popular new genetic engineering tool, generated significant unintended damage to the genome of two kinds of mouse cells and one kind of human cell — including large deletions and complex rearrangements of genetic material — in recent research conducted by a major British research institute.

The results from the Wellcome Sanger Institute suggest that researchers using CRISPR-Cas9 technology to engineer human gene therapies should very carefully analyze their own results to rule out such serious unintended effects before providing such new therapies to patients, according to the study's authors. The study was published in the July 16, 2018 issue of *Nature Biotechnology*.

The Wellcome Sanger researchers conducted a series of experiments involving embryonic stem cells and blood-making cells from mice and also human retinal cell lines. "We show that extensive on-target genomic damage is a common outcome at all loci and in all cell lines tested," they reported. They added that they also observed unintended off-target effects, meaning at locations in the genome that they were not attempting to alter.

These results are of special relevance, given that several clinical trials with patients are already underway using cells that have been engineered using CRISPR-Cas9. It has been assumed by many researchers to be fairly specific in its actions, and, in fact, is "poised to become the gene editing tool of choice in clinical contexts," the authors added. They suggested that other researchers may have failed to detect the extent of damage caused by this tool in part because they may not have broadly enough searched for unintended effects across the genome. Another reason, they added, may be because other attempts to assess the unintended effects of CRISPR-Cas9 often have used cancer cells, rather than normal cells and tissues, which may react differently.

The genetic damage they detected, the authors concluded, may cause disease:

> In the clinical context of editing many billions of cells, the multitude of different mutations generated makes it likely that one or more edited cells in each protocol would be endowed with an important pathogenic lesion. Such lesions may constitute a first carcinogenic "hit" in stem cells and progenitors, which have a long replicative lifespan and may become neoplastic [part of a tumor] with time. . . . Results reported here also illustrate a need to thoroughly examine the genome when editing is conducted ex vivo [outside the body]. As genetic damage is frequent, extensive and undetectable by the short-range PCR assays that are commonly used, comprehensive genomic analysis is warranted to identify cells with normal genomes before patient administration.

Sources

Kosicki, Michael, Kärt Tomberg, and Allan Bradley (2018). "Repair of Double-Strand Breaks Induced by CRISPR–Cas9 Leads to Large Deletions and Complex Rearrangements," *Nature Biotechnology* vol. 36, pp. 765–71. https://doi.org/10.1038/nbt.4192

Begley, Sharon (2018). "Potential DNA Damage from CRISPR Has Been 'Seriously Underestimated,' Study Finds," *STAT*, July 16, 2018. https://www.statnews.com/2018/07/16/crispr-potential-dna-damage-underestimated/?utm_source=STAT+Newsletters&utm_campaign=f31e73f098-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-f31e73f098-150135765