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CRISPR Gene Editing Can Trigger Tumors, Two Studies Warn

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STORY AT-A-GLANCE

- CRISPR-Cas9, a form of "molecular scissors," allows for very precise DNA editing, i.e., the removal, addition or altering of sections of a DNA sequence
- While CRISPR-Cas9 gene editing is more precise in that you can target a specific area of the genome, two recent studies warn the gene editing process can trigger cancer
- When you cut the two double helix strands of the DNA, the injury triggers the cell to activate a gene called p53 — a "biochemical first-aid kit" that either mends the DNA break or signals the cell to self-destruct; so, either the genome edit is mended or the cell dies
- In instances where the cell survives and accepts the edit, it does so because it has dysfunctional p53, and p53 dysfunction has been shown to significantly increase your risk of cancer
- CRISPR stock dropped between 5% and 13% within days of the findings' publication

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The discovery of the gene editing method known as CRISPR[1] eventually led to a novel gene editing tool called CRISPR-Cas9,[2] a form of molecular scissors that allows for far more accurate DNA editing for the removal, addition or altering of sections of a DNA sequence. A layman's explanation of the technology is presented in the video above.

CRISPR is the acronym for clustered regularly interspaced short palindrome repeat, and its function was initially discovered in 1993 by Spanish researcher Francisco Mojica.[3] Mojica hypothesized CRISPR is an adaptive immune system, which has since been confirmed.

Two decades later, in 2013, the technology known as CRISPR-Cas9 was successfully used to edit the genome in eukaryotic cells for the first time, demonstrating targeted genome cleavage could be achieved in mouse and human cells.

As reported by Nature[4] in 2016, "Researchers use CRISPR-Cas9 to make precise changes to genomes that remove or edit a faulty gene. It has worked on nearly every creature on which they have tested it, including human embryos."

In the wake of these discoveries, a number of CRISPR-based companies have sprung to life with the hopes of furthering gene editing in everything from food and medicine[5] to eventually producing "designer babies" that have had unwanted genetic traits edited out.

However, while CRISPR-Cas9 gene editing is more precise in that you can target a specific area of the genome, two recent studies call for a rethink, as the process of gene editing can trigger cancer.[6,7] As noted by STAT News[8] these findings could be "a potential game-changer for the companies developing CRISPR-based therapies."

CRISPR Editing Triggers Tumor Growth

The two studies[9,10] were published in Nature Medicine, and present a sobering warning to scientists hell-bent on defeating nature. It appears that cells whose genomes are successfully edited by CRISPR-Cas9 have carcinogenic potential, turning them into proverbial ticking time bombs. As reported by STAT News:[11]

> *"CRISPR has already dodged two potentially fatal bullets — a 2017 claim[12] that it causes sky-high numbers of off-target effects was retracted[13] in March, and a report[14] of human immunity to Cas9 was largely shrugged off as solvable.[15] But experts are taking the cancer-risk finding seriously."*

Indeed, CNBC[16] and Market Watch[17] reported CRISPR stock dropped between 5 and 13% within days of the findings' publication. The two studies — one performed by scientists at the Karolinska Institute[18] in Sweden and Cambridge University in the U.K., the other by the Novartis Research Institute in Boston[19] — both found the same thing.

When you cut the two double helix strands of the DNA, the injury triggers the cell to activate a gene called p53, described as a "biochemical first-aid kit" that either mends the DNA break or signals the cell to self-destruct. As noted in the featured article, "Whichever action p53 takes, the consequence is the same: CRISPR doesn't work, either because the genome edit is stitched up or the cell is dead."

Cutting the Genome Activates Repair-or-Kill Mechanism

According to the Novartis team, p53 lowers CRISPR efficiency seventeenfold in pluripotent stem cells — stem cells that can turn into virtually any other cell and are therefore a primary candidate for the development of therapies targeted at a wide array of diseases. This helps explain previous findings that suggest CRISPR isn't nearly as efficient as initially hoped.

According to STAT News, "CRISPR is woefully inefficient, with only a small minority of cells into which CRISPR is introduced, usually by a virus, actually having their genomes edited as intended." Emma Haapaniemi, who led the Swedish team, noted that since cutting the genome is what activates p53, genome editing becomes a very difficult undertaking.

Importantly, both teams discovered that in instances where the cell actually survives and accepts the edit, it does so because it has dysfunctional p53, and p53 dysfunction has been shown to significantly increase your risk of cancer. Mutations of this particular gene are thought to be responsible for:[20]

- 50% of ovarian cancers
- 43% of colorectal cancers
- 38% of lung cancers

- 33% of pancreatic, stomach and liver cancers
- 25% of breast cancers

"By picking cells that have successfully repaired the damaged gene we intended to fix, we might inadvertently also pick cells without functional p53. If transplanted into a patient, as in gene therapy for inherited diseases, such cells could give rise to cancer, raising concerns for the safety of CRISPR-based gene therapies," Haapaniemi told the New York Post.[21]

The Catch-22 of Gene Editing

In other words, even if scientists become exceptionally adept at accurately cutting out and inserting new DNA sequences, when the process works as intended, it's because p53 fails to do its job, which significantly raises the risk of cancer formation.

It's a real Catch-22 that puts a significant damper on the idea that we can customize the genome to our own liking simply by cutting and splicing DNA sequences. It appears nature has built-in fail-safe systems for this eventuality. As noted by the Novartis team, "it will be critical to ensure that [genome-edited cells] have a functional p53 before and after [genome] engineering."

All hope is not lost, however. It's possible that these findings may be applicable only when you replace disease-causing DNA with a healthy DNA sequence, and not when you're just removing a piece of the DNA sequence, so CRISPR may still be useful in some instances. As explained in the featured article,[22] the genome can be edited with CRISPR in two different ways:

1. Non-homologous end joining (NHEJ), also referred to as gene disruption. This is where a disease-causing section of DNA is simply cut out and not replaced. NHEJ is currently being used by CRISPR Therapeutics in their development of a treatment for sickle cell disease. Others are working on treatments for cystic fibrosis and severe immunodeficiency using gene disruption

2. Homology-directed repair (HDR) or gene correction. Here, the disease-causing section is cut out and replaced with a healthy section. HDR is being investigated for the treatment of muscular dystrophy and other diseases

Stem Cell DNA Are Most Difficult to Edit

At present, any therapy based on CRISPR technology would have to involve three steps: Remove cells from your body, alter the DNA and then reintroduce the cells into your body. However, CRISPR-based companies are also working on technologies for editing the genome right inside your body, without having to take out and reinsert the cells.

This presents a far greater challenge, and while it would broaden the range of diseases that could be addressed, it may also be far more dangerous with any number of potential side effects — including cancer, according to these two studies.

For now, it appears NHEJ doesn't trigger p53 to undo the edit when used in regular cells, which companies using gene disruption take as a hopeful sign. (CRISPR Therapeutics, which has entered a joint venture with Bayer to create drugs for blood disorders and blindness using CRISPR technology, is one of these companies.)

Therapies using CRISPR base editing, a technique that does not cut the two helix strands that trigger p53, may also avoid the carcinogenic problem posed by p53.

Stem cells, on the other hand, seem to have more robust defenses against genetic alterations. The Novartis team showed that p53 needs to be inactivated both for NHEJ and HDR to be a success when using stem cells. And, as noted by STAT News, "That could be an issue for therapies using CRISPR'd stem cells: The same dysfunctional p53 that allows CRISPR to work its magic also makes cells likely to become cancerous."

Unintended Side Effects Abound in Genetic Engineering

CRISPR may be far more sophisticated and precise than previous genetic engineering techniques, but precision is no guarantee of safety, as these two studies reveal. There

have been many occasions where a genetically engineered (GE) crop has been shown to be unexpectedly toxic or allergenic when the conventional crop had no such issues.

The reality is that scientists really don't know what side effects may be produced by DNA tampering. The effects are extremely unpredictable.

Even CRISPR, for all its precision, creates off-target effects. This is a serious concern not only in medicine but also in agriculture. As noted in a recent paper,[23] "CRISPR technology is erasing barriers to genome editing and could revolutionize plant breeding."

In plants, the potential for unintended effects such as toxicity and allergic potential remain high even with CRISPR technology, for the simple fact that when you alter one or two genes in a genome the side effects ripple through the whole genome.

A new protein could be created in the process that could be toxic or allergenic, or you could change the biochemical pathways of a plant, making it less nutritious or more toxic. Moreover, most GE plants are engineered for the express purpose of either expressing an internal insecticide or to tolerate direct herbicide application. So even if CRISPR technology improves the specificity of the genetic alteration, the toxic effects of herbicides and insecticides in the plant remain an issue.

As noted by Claire Robinson, editor of GM Watch and coauthor of "GMO Myths and Truths," the risk of unintended consequences is so high that even if scientists restricted the insertion of genes into a plant to the very same species, say from corn to corn, these risks still would not disappear. Robinson explains:

> *"The important thing when you're genetically engineering a plant is the new context of the gene that you're putting in. Even if you take the gene out of apples and put it into apples as is the case with the Arctic genetically modified apple, you don't really know what that's doing, because all of a sudden the gene is in a new context."*

Plan for 'Designer Babies' Could Prove Disastrous

The risks increase exponentially when you start talking about making "designer babies." As mentioned earlier, the enzyme called Cas9 allows for very precise gene alterations, and has been successfully tested in human embryos. Cas9 uses a specific RNA molecule as a guide to cut the DNA at the precise target. However, as noted by Nature,[24] Cas9 sometimes creates unwanted mutations.

This is yet another puzzle piece that would need to be perfected before we start designing humans without genetic predispositions for disease. Over and beyond that, there's also the fundamental issue of epigenetics, which posits that your environment (diet, lifestyle, toxic exposures and even emotional states) influences how your genes are expressed.

One could argue that it would be far wiser (and easier) to work on eliminating toxins from our food, water, environment and everyday products and focus on lifestyle strategies that support health and well-being rather than trying to design a disease-free human from scratch by tinkering with the genetic code.

If you think designer babies are a far-fetched idea, think again. In December 2015, hundreds of scientists and ethicists met in Washington, D.C., at the U.S. National Academy of Sciences (NAS) to discuss the sanctioning of germ-line engineering, meaning the altering of DNA in sperm, eggs and embryos to remove or correct genetic defects.[25]

Last year, a report[26] by the NAS and the National Academy of Medicine concluded that gene editing of human embryos to prevent disease "might be permitted, but only following much more research" on risks and benefits, and "only for compelling reasons and under strict oversight."

One "compelling reason" given by committee co-chair Alta Charo, bioethicist at the University of Wisconsin in Madison, would be if both would-be parents have serious genetic disease, and gene editing of the embryo would be "the last reasonable option" to have a healthy biological child.

Still, while designer babies are not in our immediate future, considering the pace at which scientific progress moves, it seems reasonable to suspect that genetic engineering of humans will eventually come to pass. CRISPR-Cas9 provides the means to do so already,[27] but that doesn't mean we'll ever know enough about gene editing to actually do a good job of it.

Clearly, there are as many hazards as there are opportunities for this and future gene editing technologies. Genetic diseases and defects could potentially be eradicated, and any number of diseases might be cured once they strike with this technology. On the other hand, introduced mutations or side effects might leave a child worse off, or cause unintended generational effects. At that point, it might be too late to fix or stop the problems we created.

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