

Light-activated 'CRISPR' triggers precision gene editing and super-fast DNA repair

June 17 2020



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In a series of experiments using human cancer cell lines, scientists at Johns Hopkins Medicine say they have successfully used light as a trigger to make precise cuts in genomic material rapidly, using a molecular scalpel known as CRISPR, and observe how specialized cell proteins repair the exact spot where the gene was cut.

Results of the experiments, published June 11 in *Science*, not only reveal new details about the DNA [repair](#) process, but also are likely, the researchers say, to speed up and aid understanding of the DNA activity that typically causes aging and many cancers.

"Our new system of gene editing allows for targeted DNA cutting within seconds after activation. With previous technologies, gene editing could take much longer—even hours," says postdoctoral fellow Yang Liu, Ph.D., a member of the Johns Hopkins Medicine research team.

The powerful CRISPR tool has, in recent years, enabled scientists to easily change, or "edit," DNA sequences and alter gene functions to speed the pace of research on gene-linked conditions.

Adapted from a naturally occurring gene editing system found in bacteria, CRISPR uses small sequences of genetic material called RNA as a kind of guide that is coded to match and bind to a specific sequence of genomic DNA within a cell. The CRISPR molecule also contains an enzyme called Cas9, which acts as the scalpel to cut out the DNA sequence. Then, the cell uses its own enzymes and proteins to repair the sliced DNA, often adding DNA sequences that scientists slip into the cell.

Liu says that studying the DNA repair process has been hampered by an inability to damage the DNA, such as by using CRISPR, in a way that's fast, precise and "on demand."

For the new experiments, the scientists modified the CRISPR-Cas9 complex by engineering a light-sensitive RNA molecule that allows the CRISPR complex to cut genomic DNA in living [cells](#) only when exposed to a particular wavelength of light.

"The advantage of our technique is that researchers can get the CRISPR machinery to find its target without prematurely cutting the gene, holding back its action until exposed to light," says Johns Hopkins M.D.-Ph.D. candidate Roger Zou, also a member of the research team. "This allows researchers to have far more control over exactly where and when the DNA is cut," he adds.

Other research teams have experimented with both drugs and light activation to control CRISPR timing, says Taekjip Ha, Ph.D., Bloomberg Distinguished Professor of Biophysics and Biophysical Chemistry, Biophysics and Biomedical Engineering at Johns Hopkins University, and a Howard Hughes Medical Institute investigator. His team's experiments differ by improving the precise timing of CRISPR cuts and examining how quickly proteins repair the DNA damage.

For the current study, the Johns Hopkins team, led by Ha and Bin Wu, Ph.D., assistant professor of biophysics and [biophysical chemistry](#) at the Johns Hopkins University School of Medicine, delivered an electric pulse to cultures of human embryonic kidney cells and bone cancer cells, which opened pores in the cell membrane and allowed the CRISPR complex with the light-activated RNA molecule to slide into the cells. Then, the scientists waited 12 hours for the CRISPR complex to bind to a targeted spot on the genomic DNA.

When they shined a light on the cells, they tracked the amount of time it took for the CRISPR complex to make the cut.

The team found that within 30 seconds of shining the light on the cells, the CRISPR complex had cut more than 50 percent of its targets.

To further examine the timing of DNA repair, the Johns Hopkins scientists tracked when proteins involved in DNA repair latched on to the DNA cuts. They determined that repair proteins started their work within two minutes of the CRISPR activation, and the repair was completed as early as 15 minutes later.

"We have shown that light-activated gene cutting is very fast, and it has potentially wide applications in biomedical research." says Ha.

"Revealing the timing of CRISPR gene cuts allows us to see biological processes far more precisely." Ha and the Johns Hopkins team have dubbed the technique "very fast CRISPR on demand."

Ha also noted that light-activation offers better location control than drugs that can diffuse widely in the cell.

The Johns Hopkins team also used high-resolution microscopes to "see" how repair proteins interact with the CRISPR cut site in living cells.

They used these microscopes and a focused beam of light to show that they could activate CRISPR cutting of one of two gene copies that are normally found in human cells. This capability, they say, offers opportunities for using CRISPR to study and eventually treat conditions linked to only one abnormal gene copy, such as Huntington's disease.

"There is a big research community interested in studying DNA damage and its impact," says Ha. "The technology we developed is well suited to study that."

Ha notes that scientists typically use ionizing radiation or chemicals to study DNA damage. While those methods can also be fast, he says, they are not specific to a certain genomic location.

The team has filed a provisional patent on the CRISPR technology described in this research.

More information: Yang Liu et al. Very fast CRISPR on demand, *Science* (2020). [DOI: 10.1126/science.aay8204](https://doi.org/10.1126/science.aay8204)

Provided by Johns Hopkins University School of Medicine

Citation: Light-activated 'CRISPR' triggers precision gene editing and super-fast DNA repair (2020, June 17) retrieved 6 May 2024 from <https://medicalxpress.com/news/2020-06-light-activated-crispr-triggers-precision-gene.html>

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