NEWS EXPLAINER
08 January 2018

How the immune system could stymie some CRISPR gene therapies

Researchers hoping to use a gene-editing technique to treat diseases may have to seek alternative enzymes.

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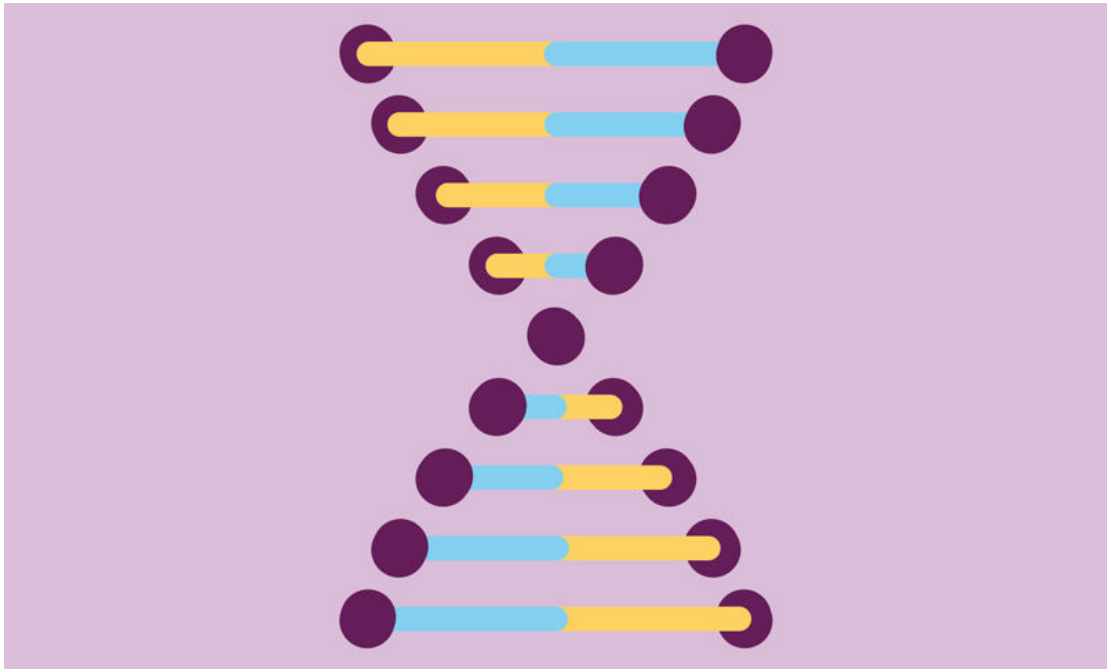

The body's own immune system could thwart some efforts to develop gene therapies based on the trendy genome-editing tool called CRISPR-Cas9, according to a study released on 5 January[1].

Hopes are high that CRISPR–Cas9 could one day be used in people to correct mutations that cause disease. But the new study, which was published on the preprint server bioRxiv and has not yet been peer-reviewed, is generating questions about whether this approach will succeed.

Nature looks at what the findings mean for the popular genome-editing system — and the academics and companies who hope to harness it to treat genetic diseases.

How does CRISPR–Cas9 work?

CRISPR–Cas9 is a primitive immune system that is found in a wide range of microorganisms. The system relies on an enzyme called Cas9, which slices DNA at a site determined by the sequence of a particular strand of RNA. Researchers can alter the sequence of that 'guide RNA' to aim Cas9 at a specific segment of DNA — raising the possibility that the system could be used to correct some genetic mutations that cause disease.

But foreign proteins such as Cas9 can also provoke lasting immune responses. And two versions of the Cas9 enzyme that are most prized by molecular biologists come from common bacteria that can live in the human body — increasing the chances that some people will have already formed immune responses against those proteins.

What did the study find?

A team of researchers led by paediatric haematologists Matthew Porteus and Kenneth Weinberg of Stanford University in California analysed blood samples from 22 babies and 12 healthy adults for immune responses to the two most commonly

used forms of the Cas9 enzyme

They found that 79% of study participants made antibodies against Cas9 from the bacterium *Staphylococcus aureus*, and 65% of them made antibodies against the enzyme from *Streptococcus pyogenes*.

In a related experiment, 46% of 13 adult participants produced immune cells called T cells that target Cas9 from *S. aureus*. No T-cell responses were found against the other form of Cas9 tested, although the researchers acknowledge that their test may not have been sensitive enough to detect them.

Why does that matter?

The body's immune responses can sabotage a gene therapy — and pose a health risk to the person receiving the treatment. Antibodies against Cas9 can bind to the enzyme in the bloodstream, before it has had a chance to act. And T cells that target Cas9 could destroy cells in which the protein is expressed, wiping out 'corrected' cells and potentially triggering a dangerous widespread attack on the body's own tissues.

Are the findings surprising?

Gene-therapy researchers are familiar with the threat posed by immune responses, and patients are sometimes screened for potential reactions to gene-therapy components before being allowed to receive a treatment.

As a result, testing for such immune reactions would probably be a part of any serious effort to develop a CRISPR–Cas9 therapy, particularly if the developers plan to petition the US Food and Drug Administration and other regulators for approval to sell their treatment.

One such company, Intellia Therapeutics of Cambridge, Massachusetts, is evaluating immune responses to its candidate therapies in rodents and non-human primates, says senior vice-president Thomas Barnes.

Even so, problems posed by immune responses have received relatively little attention in the popular press and scientific literature. Porteus says that he has been raising the issue with researchers who are interested in developing CRISPR–Cas9-based therapies. "But nobody seemed to be following up," he says.

Porteus is interested in developing treatments for sickle-cell anaemia by removing blood-forming cells from the patient, using CRISPR–Cas9 to correct them, and then injecting the cells back into the patient. Because the exposure to Cas9 takes place outside the body, the approach is unlikely to be threatened by an anti-Cas9 immune response.

But Porteus worries about what might happen in other trials. "It would be a real setback to the genome-editing field if a Cas9 therapy was given to a patient and it resulted in a toxic inflammatory response," he says. "We hope that this work will prompt people to think carefully about making sure that does not happen."

Is this the end for CRISPR–Cas9 in gene therapy?

Unlikely, given the tremendous interest in this approach and the wealth of alternative enzymes to choose from. "Another potential solution is to develop a Cas9 system from bacteria that do not colonize or infect humans," says Porteus. "I think this work will motivate those sorts of studies."

Researchers may also be able to tweak Cas9 enzymes in the laboratory to engineer forms that will escape pre-existing immune responses, he notes.

The first applications of CRISPR–Cas9 in clinical trials are likely to focus on approaches that, like those being investigated by Porteus, treat cells that have been removed from the body and are unlikely to activate an immune response.

And Barnes notes that Intellia, which is focusing on *S. pyogenes* Cas9, is developing therapies that would produce the Cas9 protein for a short period of time and only within cells, potentially limiting the chance for immune interference even when editing the genome in cells within the body.

References

Charlesworth, C. T. *et al.* Preprint at bioRxiv http://dx.doi.org/10.1101/243345 (2018).

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