Scientists use 'molecular-Lego' to take CRISPR gene-editing tool to the next level

12 December 2016

Credit: NIH

A team of researchers at Western University is playing with molecular-Lego by adding an engineered enzyme to the revolutionary new gene-editing tool, CRISPR/Cas9. Their study, published today in the *Proceedings of the National Academy of Sciences* (*PNAS*), shows that their addition makes gene-editing more efficient and potentially more specific in targeting genes.

The scientific community is buzzing with the promise that CRISPR offers for human gene-editing, opening the door to use gene-therapy to treat diseases like cystic fibrosis and leukemia.

In cystic fibrosis, for example, there is one gene mutation which causes the disease in a very large proportion of patients. If it were possible to use CRISPR to cut that mutation out of the genome, the disease could potentially be cured.

"The problem with CRISPR is that it will cut DNA, but then DNA-repair will take that cut and stick it back together," said the study's principal investigator, David Edgell, associate professor at Western's Schulich School of Medicine & Dentistry. "That means it is regenerating the site that the CRISPR is trying to target, creating a futile cycle. The novelty of our addition, is that it stops that regeneration from happening."

The Western researchers have demonstrated that the creation of a new enzyme called TevCas9, which cuts the DNA in two places instead of one, makes it much more difficult for the DNA-repair to regenerate the site of the cut. The researchers created TevCas9 by adding an enzyme called I-TevI onto the nuclease, Cas9, which is the typical enzyme used to cut DNA in CRISPR.

The study also showed that the addition of Tev shows promise at being much more specific in targeting genes and less likely to cause off-target effects in the genome, which is a significant problem for any potential therapeutic application.

"Because there are two cut-sites, there is less chance that these two sites occur randomly in the genome; much less chance than with just one site," said co-author Caroline Schild-Poulter, associate professor at Schulich Medicine & Dentistry and a scientist at Robarts Research Institute. "This remains to be tested, but this is the hope and the expectation."

More information: Biasing genome-editing events toward precise length deletions with an RNA-guided TevCas9 dual nuclease, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1616343114

Provided by University of Western Ontario

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APA citation: Scientists use 'molecular-Lego' to take CRISPR gene-editing tool to the next level (2016, December 12) retrieved 19 June 2019 from https://phys.org/news/2016-12-scientists-molecular-lego-crispr-gene-editing-tool.html

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