GENOME EDITING

Better guidance is cheaper

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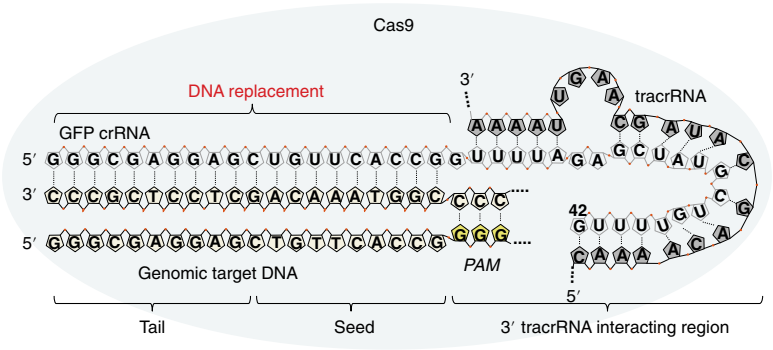

Credit: Macmillan Publishers Ltd

Genome editing allows scientists to alter an organism's DNA in a targeted manner. It is a promising technology to address societal challenges, such as prevention and treatment of human diseases or securing food and chemical supply with the help of tailored plants and microbes.

Many hopes rely on the CRISPR-Cas9 genome editing method, which is based on a defence mechanism of bacteria to fight viruses by cutting their DNA. Researchers can design guide molecules composed of crRNA and tracrRNA to instruct the endonuclease Cas9 to cut desired locations in the genome of an organism of interest (pictured). Subsequently, the cell's DNA repair machinery allows for the introduction of genomic changes at the DNA strand breakage that can lead to the desired phenotypical changes.

Now, in a systematic study, researchers at the University of Massachusetts Medical School, the Massachusetts Institute of Technology, and the Harvard-MIT Division of Health Sciences and Technology have demonstrated that the performance of this biocatalytic genome editing system can be improved by partial replacement of the crRNA sequence of the guide RNA with DNA nucleotides (pictured). In detail, they found that this modification decreases accidental mutations at non-targeted locations in human cells. Interestingly, at the same time, similar levels of successful mutations at desired locations were maintained, which was not achieved in previous experiments using truncated and chemically modified guide RNAs. Chimeric DNA–RNA guides or even all-DNA guides are from particular interest, because DNA nucleotides are distinctively cheaper in commercial oligonucleotide synthesis compared to RNA nucleotides.

In conclusion, guide molecules play a central role to achieve a high performance of CRISPR genome-editing tools. Partial replacement of RNA by DNA nucleotides in the guide molecule provides a strategy to reduce both the cost and the off-target genome editing by CRISPR–Cas9, important aspects for its use in research and medical application. Further improvements might be achieved by engineering Cas9 to tolerate a higher DNA content as well as by expanding the chemical and structural diversity of the guide sequences.

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