Genome editing

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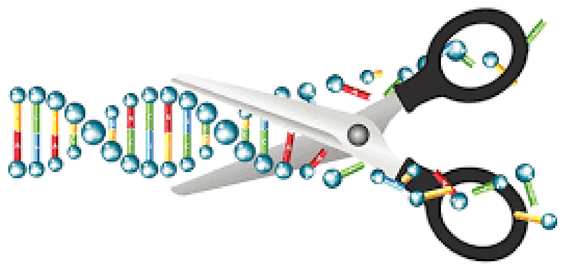
What is Genome Editing and what is it used for?

Genome editing is a way of making specific changes to the DNA of a cell or an organism. An enzyme cuts DNA at a specific, and when this is repaired by the cell a change or 'edit' is made to the sequence.

Genome editing could be used to edit the genome of an organism. It is used for research, so changing the DNA in cells or in organisms can help understand their biology and how they work. Genome editing can treat disease, as it is possible to modify human blood cells that are put into the body to treat conditions such as leukemia and AIDS. This technique is used to genetically modify crops which improve their yields and resistance to disease and drought.



History of Genome Editing

Genome editing has been a heavily studied field for a number of years with an ultimate goal of specificity to limit off target effects. The first engineered nuclease technology, Zinc Finger, was presented in a 1991 publication by Pavletich and Pabo in the journal Science. Zinc Finger was the predominant genome targeting technology for over 10 years, but over time drawbacks to the system emerged. Certain nucleotide triplets could not be targeted, and interactions within a zinc finger array could reduce specificity.

Types of genome editing

Small DNA changes:

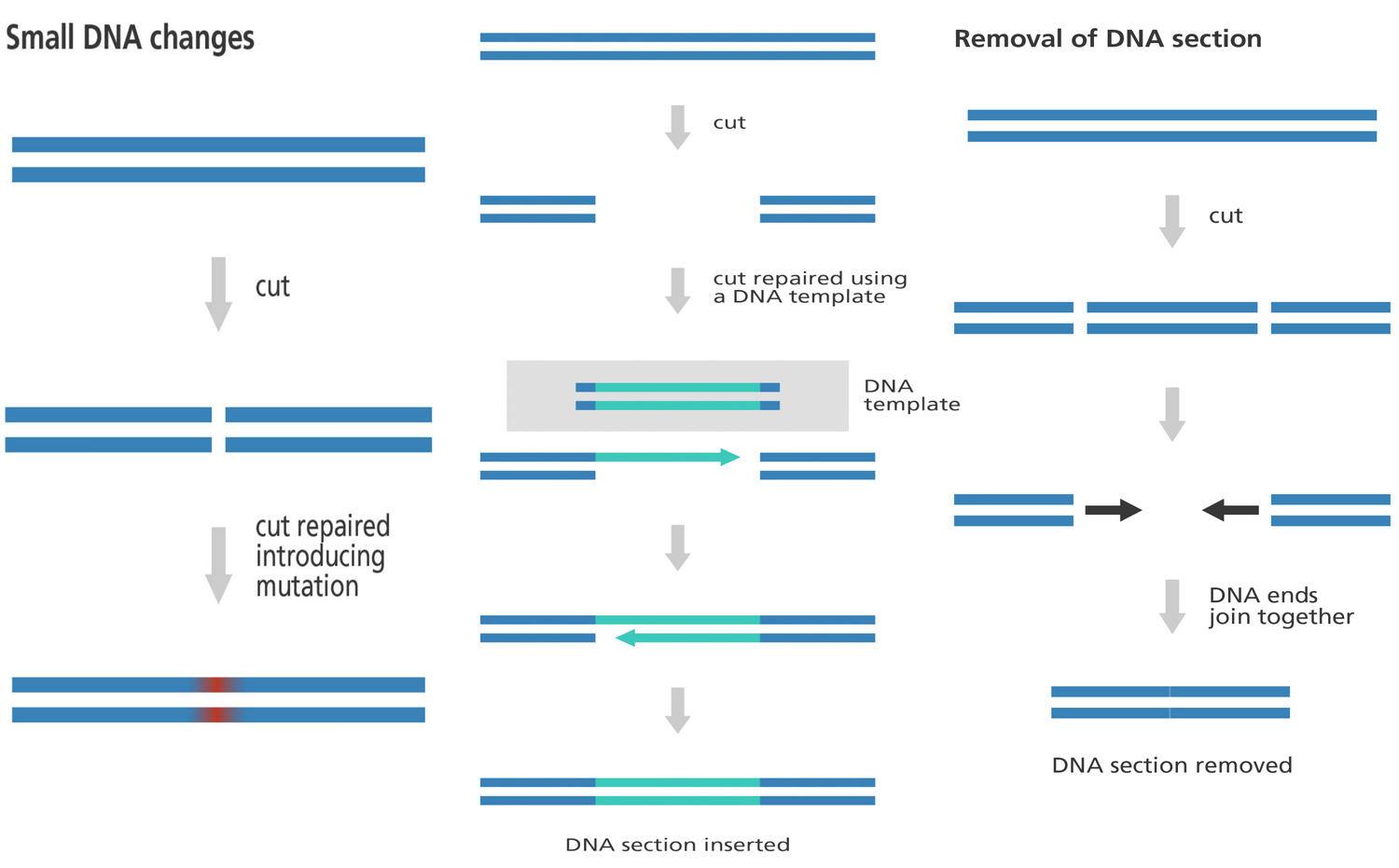
- Nuclease enzyme is engineered to cut at a specific location in the DNA.
- Cell's normal DNA repair machinery will recognise the damage and join the two cut ends of DNA back together.
- Simple repair process isn't 100% perfect and few bases are lost or added around the site of the cut when it is repaired.
- Small change in DNA will affect the function of that section of DNA, and so a gene won't function properly or function at all.

Insertion of section of DNA:

- Natural DNA repair system can be hijacked to insert a section of DNA into a genome by genome editing.
- Genome editing can take advantage of this DNA repair system to 'trick' the cell into inserting a section of DNA.

Removal of a section of DNA:

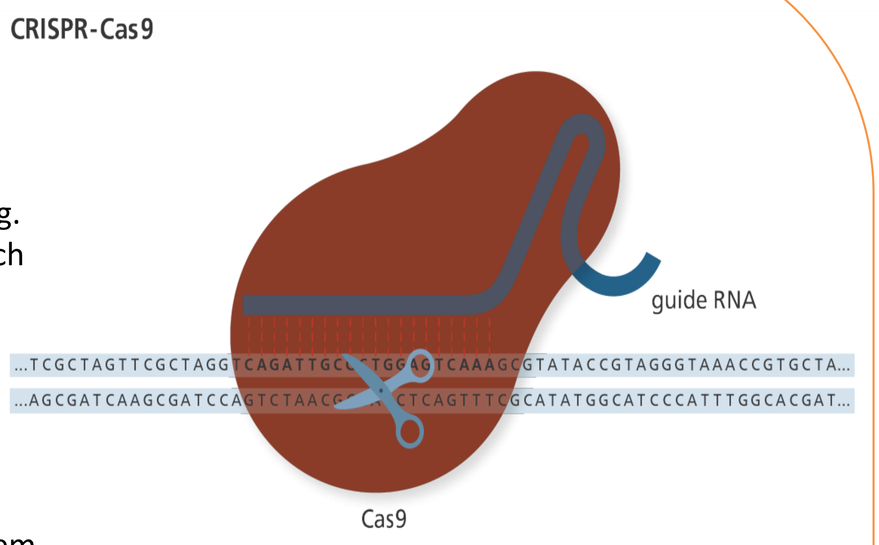
- To remove section of DNA, nucleases are engineered making cuts in the DNA either side of the section that we want to remove.
- After the engineered nucleases cut the DNA, the cell's normal DNA repair machinery will recognise the damage but may mistakenly join the wrong ends of DNA together, removing the DNA in between two cuts.



Genome editing systems

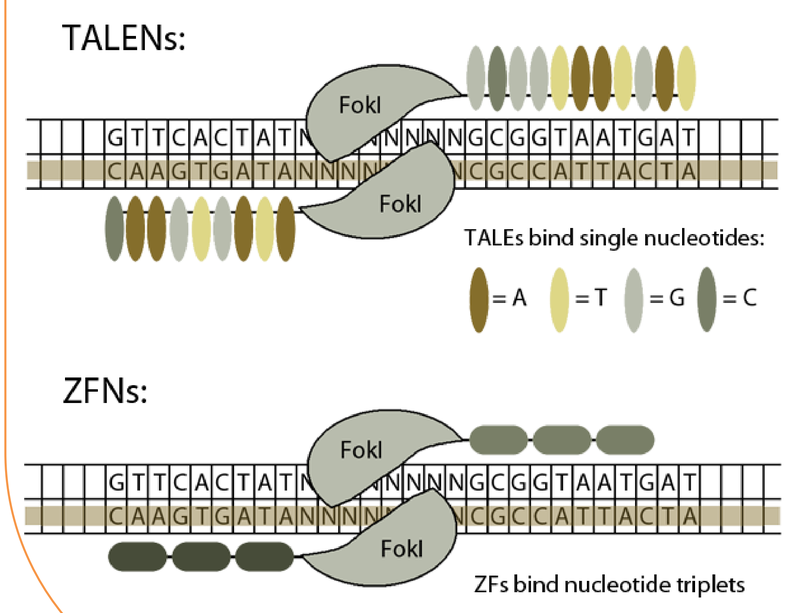
CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9):

- CRISPR is the most common, cheap and efficient system used for genome editing.
- A DNA-targeting part of the system which consists of an RNA molecule, or 'guide,' designed to bind to specific DNA bases through complementary base-pairing.
- Cas9 is the nuclease part that cuts the DNA.
- The CRISPR-Cas9 system was originally discovered in bacteria that use this system to destroy invading viruses.



TALENs (Transcription activator-like effector nucleases):

- DNA-binding domain of TALENs is made of transcription activator-like effector domains.
- There are four different TALE domains, one for each DNA base, so they can be engineered to bind to specific DNA sequences much more easily than ZFNs.
- The nuclease part of TALENs is normally a FokI nuclease, which cuts the DNA.
- Two FokI molecules must come together to make a cut in the DNA, so two TALENs are made, one for each strand.



ZFNs (Zinc-finger nucleases):

- DNA-binding part of ZFNs is made of zinc-finger proteins, which bind to about 3 DNA bases. Different combinations of zinc-finger proteins binds to different sequences of DNA.
- Nuclease part of ZFNs is normally a FokI nuclease.
- Two FokI molecules come together to make a cut in the DNA, so a pair of ZFNs are made, one binding to each strand.

How does genome editing work?

Genome editing uses a type of enzyme called an 'engineered nuclease' which cuts the genome in a specific place. Engineered nucleases is made up of two parts:

- A nuclease part that cuts the DNA.
- DNA-targeting part that is designed to guide the nuclease to a specific sequence of DNA.

After cutting the DNA in a specific place, the cell will naturally repair the cut. We can manipulate this repair process to make changes to the DNA in that location in the genome.

References

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