A NEW SIBLING FOR CRISPR-CAS9: CAS13

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Brief message

Hi everyone! My name is Femke van Hout, and I am a master's student from the Molecular Mechanisms of Disease program. I have been an editorial editor for RAMS since March 2020 but I will unfortunately 'retire' this summer after my graduation. I have greatly enjoyed being part of RAMS, and I have learned a lot about a diverse range of topics. Thanks to writing for RAMS, I can now tell you everything about our microbiome and (non-existing) sex pheromones! For this brief message, I chose the hot topic of CRISPR/Cas systems, but instead of the well-known CRISPR/Cas9 I wrote about CRISPR/Cas13. Even though the molecular mechanisms may seem a bit daunting at first, I hope that this brief message can inspire you about the beauty of CRISPR/Cas systems!

The last decade marks the exciting revolution of CRISPR/Cas9 genome editing. While the revolution still continues with further development and refinement of the Cas9 systems, the first patients are already receiving Cas9-based treatments. The Cas9 enzyme is a so-called 'RNA-guided DNA nuclease', which means that Cas9 is directed by RNA, the guide RNA, to find and cut the complementary target DNA. As this cutting mechanism is very precise and programmable, Cas9 can in theory be used to change any DNA sequence. Many diseases could potentially be cured, including sickle cell disease, Duchenne muscular dystrophy, and Huntington's disease [1]. However, changing someone's DNA could have severe implications regarding safety and ethics.

Luckily, it turns out that Cas9 has many siblings. Among them is the recently discovered Cas13 that cuts RNA instead of DNA, making Cas13 an 'RNA-guided RNA nuclease' (Figure 1) [2]. This means that Cas13 can be used to cut RNA encoding for disease-causing proteins. In this way, the production of the disease-causing protein is prevented without modifying the genome!

The first successes with Cas13 in human cell lines and mice have recently been published [3]. In one important example, the mRNA encoding for the KRAS protein, which is often found to carry mutations in pancreatic cancer, was targeted [3]. However, no drugs exist to target the KRAS protein. Cutting KRAS mRNA would therefore be an effective strategy to prevent the production of the mutant protein. With guide RNAs that recognise the KRAS mRNA, Cas13 reduced the mRNA level by 94%. This resulted in the apoptosis of cancer cells *in vitro* and tumour shrinkage in the mice model.

The fact that Cas13 can prevent the production of disease-causing proteins without changing the DNA is a very important advantage of Cas13 over Cas9. Moreover, Cas13 can be used to cure diseases for which there is no DNA to target. The vast majority of the viruses that cause human disease have an RNA genome. Apart from the retroviruses, these RNA viruses do not have any DNA intermediate in their replication cycle. Therefore, Cas9 cannot be used to target these viruses, while Cas13 can. With guide RNAs targeting influenza virus A and SARS-CoV-2, Cas13 has already been shown to effectively degrade the viral RNA, mitigating the viral infection in human cell lines [4]. All in all, the Cas13 enzyme has great potential for the treatment of various human genetic diseases, cancers, and virus infections.

References

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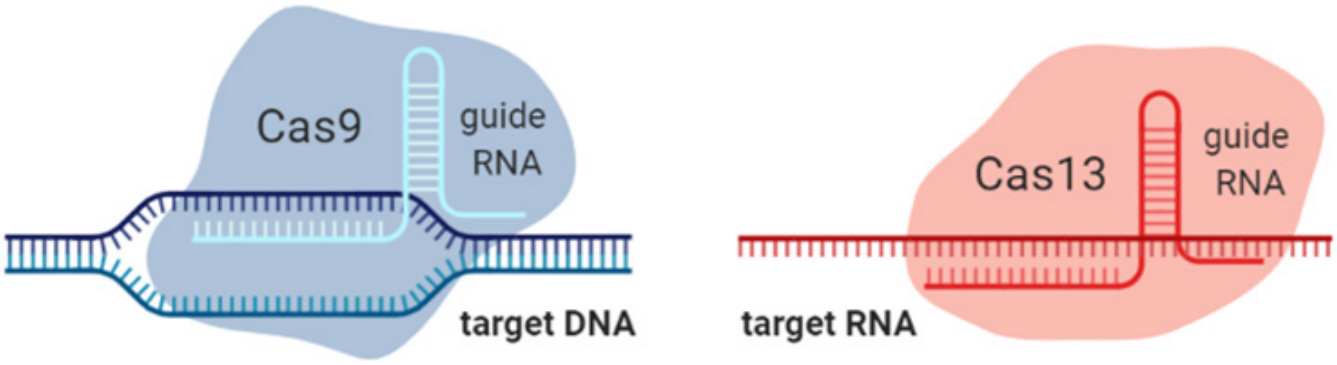

Figure 1: *Schematic representation of the Cas9 and Cas13 enzymes with guide RNA and target DNA/RNA, created with Biorender.com.*

EXAM QUESTION

Question 10

Do you want to test your knowledge about genetics? Then, try to answer the following question.

DNA and RNA, both amino acids, are very similar. Yet, there are a few differences. One typical difference is that RNA...

A. contains deoxyribose as a sugar.
B. is not capable of forming a double helix.
C. contains uracil as a base.

The answer to this question can be found on page 34 in this journal.