Can The CRISPR-Cas9 Enzyme Free An Individual Of Inherited Cardiovascular Disease?

Rationale

The research question that was decided was formed from the claim 'Crispr can produce individuals who are free of genetic disease.' An article posted on the Morning Edition mentioned that a New York scientist conducted gene-editing experiments which, although raised some ethical concerns, could someday prevent many inherited diseases. Before the final question could be developed, numerous elements from the claim needed to be considered and broken down into key questions. Examples of these include ‘What is CRISPR?’, ‘What are genetic diseases?’ and ‘How can CRISPR prevent genetic disease?’. Through this research, it was found that CRISPR is a repeated sequence of nucleotides and the enzyme called Cas9 uses these sequences to recognize specific strands of DNA (Source 8). It was also found that genetic diseases are the result of changes or mutations in DNA (Source 2) and according to 2017 statistics from W.H.O, cardiovascular diseases are the highest cause of death globally. While not all heart diseases are genetic, inherited cardiac disorders include arrhythmias, congenital heart diseases, and cardiomyopathy (Source 9). From this information, the final research question was formed, ‘Can the CRISPR-Cas 9 enzyme reduce the risk of inherited cardiovascular diseases in an individual?’ While genetic cardiovascular diseases are unfortunate to possess, the implementation of CRISPR could save millions of lives from this deadly condition.

Scientists have discovered that individuals who had potentially high levels of low-density lipoprotein (LDL) all had a common mutation in a gene called PCSK9. This gene is responsible for encoding an enzyme that regulates levels of LDL, but this mutation caused an increase in the enzyme’s activity which raised the level of cholesterol in the bloodstream. In 2014, Musunuru and his team experimented with mouse liver where a CRISPR-Cas9 system was directed against the PCSK9 enzyme. As shown in Figure 1, the results concluded that there was a 90% decrease in the level of PCSK9 and a 35-40% decrease in blood LDL cholesterol (Source 1). The experiment also proved that the human gene of PCSK9 could also be switched off through this method (Source 3). Although there are many similarities between mouse liver and human liver, there are still many differences which would decrease the accuracy or possibly produce side-effects.Figure 1: Effects of CRISPR genome editing on mice

There have also been advances in research regarding CRISPR-Cas9 with the support of induced pluripotent stem cells (iPSCs). These are cells derived from skin or blood cells that have been genetically reprogrammed to an embryonic stem cell-like state. This system has allowed scientists to correct genetic mutations in iPSC-related disease models and has been applied to the study of various cardiac diseases. Wang generated iPSCs from Barth syndrome patients and identified structural and functional abnormalities of the tafazzin (TAZ) gene. Through this discovery, Wang’s team uncovered that the antioxidant MitoTEMPO was efficient for reducing the activity of the mutated TAZ gene back to normal. Another example includes Yamamoto creating an iPSC clone from an individual with Long QT syndrome which had a mutation in the heterozygous Calmodulin 2 enzyme. More importantly, the allele was successfully removed with CRISPR-Cas9 and the abnormal electrophysiological properties

were reduced (Source 4). With the help of iPSCs, CRISPR has also successfully restored other mutated genes in stem cell models which could easily soon be applied to real-life humans.

[image:]For the CRISPR-Cas9 to successfully locate and alter the correct the DNA region, the Protospacer Adjacent Motif (PAM) needs to be present. As shown in Figure 1, the PAM sequence is 2-6 base pairs in length and is required to allow the Cas9 nuclease to cut and separate the DNA strand. However, this section of DNA only occurs in approximately every 8 base pairs in the genome and CRISPR editing location is severely limited by the reduced presence of PAM (Source 7). In other words, the DNA regions that do not contain PAM cannot be edited with the CRISPR-Cas9 enzyme and PAM is almost equally as important as Cas9 to allows this technology to be implemented. However, there are many solutions that scientists can develop to expand the operating area of the genetic experiments, but this is still yet to be solved and will require time to be investigated.Figure 2: How Cas9 Locates Gene through PAM

A wide variety of sources were used to draw the conclusion, all of which were reliable and relevant. The journal articles and websites that were used both contained lots of relevant information and were all written by qualified scientists, researchers, and journalists. Therefore, the conclusion is valid and accurate.

However, these sources contained a little too much information and the investigation would have considerably improved if the research question was more specific. An improved version could have been, ‘Can the CRISPR-Cas9 enzyme free an individual of inherited hypocholesterolaemia?’ The claim could be further explored by looking at the effects of CRISPR on chromosomal genetic diseases. These inherited diseases begin at an early age and can heavily impact a human on their feelings and physicality.

The analysis has proven that there is significant evidence the CRISPR-Cas9 enzyme could free an individual of inherited cardiovascular disease. Through the discovery of the PCSK9 and TAZ genes researchers have identified which DNA strands to target with CRISPR-Cas9 to combat inherited cardiac diseases. With the assistance of induced pluripotent stem cells (iPSCs), scientists have been able to insert and modify genetic mutations into clone models of these diseases. However, the Protospacer Adjacent Motif DNA sequence is required to allow the DNA separated and operated on with CRISPR-Cas9. While this is a minor issue, with a little more time scientists will be able to avoid this problem and instead of individuals having to take pills for the rest of their lives, a single insertion of CRISPR-Cas9 will be able to cure all inherited cardiovascular disease. In conclusion, CRISPR can produce humans are free of cardiovascular disease and with this technology, other inherited diseases could also be cured.

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