Developing CRISPR-Cas9 as a therapeutic tool to treat inherited genetic disorders

By Daniel Robinson

Generating site specific genetic modifications with relative ease has long been a desire of researchers for a variety of reasons, ranging from the study of specific proteins in biochemical pathways, to researching important regulators in development. Of particular interest to the medical field, the ability to correct genetic abnormalities within a person's genome would, for the first time, offer viable cures to fix genetic diseases.

With the recent development of clustered, regularly interspaced, short palindromic repeats (CRISPR) into a usable technology, scientists throughout the world now have the opportunity to generate specific gene modifications. Known as CRISPR-Cas9, this system uses engineered RNAs in combination with nucleases to generate these genetic modifications within the genome of a specific host organism (1).

One attractive application of CRISPR-Cas9 is its use in the development of therapies to correct genetic disorders. At The Hospital for Sick Children in Toronto, Dr. Ronald Cohn has been doing just that - studying the extent to which CRISPR-Cas9 can be used as a therapeutic tool to treat inherited genetic disorders.

When asked about the benefits of CRISPR-Cas9 as a genome editing tool over other technologies (such as TALEN and Zinc Finger Nucleases), Dr. Cohn explains that "CRISPR technology is overall more precise, easier to use and also cheaper" (2). Given the advantages of this system and its ability to easily and precisely edit a genome, Dr. Cohn adds that it is "a game changer as we are now for the first time able to conceptualize how to actually fix gene mutations" (2).

In recently published work, Dr. Cohn showed that CRISPR-Cas9 can directly correct genes in cultured muscle stem cells from patients affected by Duchenne Muscular Dystrophy (DMD) (3). Dr. Cohn explains that his research efforts are focused "on removing duplications in the dystrophin gene as a means to restore the full length, wild type protein". Because DMD is caused by an incorrect expression of the dystrophin protein, using CRISPR-Cas9 to fix the defects and correctly express the dystrophin protein could become a novel way of treating this disease.

Further, Dr. Cohn and his research team successfully "developed a new methodology of correcting a splice site mutation independent of homology directed repair" (2) on the DMD muscle stem cells. In essence, Dr. Cohn and his lab were able to successfully correct the genetic mutation in the human DMD muscle stem cells, which allowed for the production of full length and functional dystrophin.

Despite the current progress towards developing CRISPR-Cas9 as a therapeutic tool, there is still work that remains to assure its safety for use in patients. Precisely, Dr. Cohn warns that "we don't know enough about potential off target effects and [if] there might be an immune reaction toward the protein Cas9" (2). A series of optimizations with in vivo experiments in animal models must also be performed to optimize the efficacy of this system.

The work performed in Dr. Cohn's lab has provided a big step in establishing the use of CRISPR-Cas9 technology as a method to correct genetic abnormalities within an affected person's genome. Doing so would directly fix the inherent cause of the genetic disorder instead of treating the symptoms – all while providing an improved quality of life in affected persons and reduced financial and time strains on the Canadian healthcare system. ■

References

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