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CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 in Treatment of Genetic Hematological Diseases

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Editorial

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Keywords

CRISPR; Treatment; DNA; Diseases

Abbreviations

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; NHEJ: Non-Homologous End Joining; HDR: Homology-Directed Repair; PAM: Protospacer Adjacent Motif.

Editorial

Blood is an important connective tissue in the body and not escaped by diseases as seen in other organs. Genetic blood disorders such as sickle cell anemia and β-thalassemia is worldwide problem due transfusion dependency which ultimately led to transfusion related chronic complication such as Hepatitis B & C, HIV and iron overload lead to hemochromatosis etc. Further regular blood transfusion have load to the community for regular supply of safe blood to these patients. There is a lot of innovation and research in this field of hematological for diagnosis and treatment. However these advancement and innovation bring significant challenges that must be explored. This editorial will discuss the role of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) to change the concept of disease and its treatment.

Novel Approach

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) was a new discovery in science and got attention when two of the scientist Jennifer Doudna and Emmanuelle Charpentier were awarded Nobel Prize in Chemistry in 2020 [1]. It is one of the seminal innovations in this field. The advent of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) – Cas9 gene editing technology was versatile technology used to edit the genomes by altering the DNA sequence and gene function to cure the genetic hematological problems like sickle cell anemia and β thalassemia. There is promising results to correct the genetic mutation at their source in early clinical trials. Basically evolved CRISPR is short sequence of repetitive DNA segments in bacteria and acts as innate immune response by sorting the DNA fragments from past infections. Cas9 protein particularly functions as molecular knife to cut DNA at particular location. This cutting is guided by synthetic guide RNA (gRNA) matched the target gene's DNA sequence. It creates a double stranded sequence break followed by DNA repair process which disabled or introduce the new genes. Applications of CRISPR are studying gene functions, developing treatment for genetic disorders in diseases. It can also be used in agriculture for enhancing crop trait and engineered microbes for industrial use. It may be a revolutionary tool in genetic engineering and highlighted the importance of addressing associated challenges [2]. Kato-Inui, et al. [3] discussed that homology-directed repair (HDR) and non-homologous end joining (NHEJ) products changed the guide RNA (gRNA) and Cas9 protein variant with enhance conformational checkpoint in HEK293T and HeLa cells and suggested that original bacterial CRISPR/Cas9 system was not perfect for HDR induction genome editing rather they said that Cas9 checkpoint can optimized the HDR/NHEJ ratio which enhance the system efficacy [3]. Gene therapy for Chronic Obstructive Airway Disease , SCID Xi, β thalassemia and glioblastoma were well started in 2000 but got set back due to death of some clinical trial participants. The discovery of CRISPR/Cas9 re-evolves the gene therapy closer to reality allowing nuclear and mitochondrial DNA editing. Significance of studying the disease that lack in

vitro model such as neurodegenerative diseases, CRISPR/Cas9 technique played a pivotal role as it involves adult stem cells in pluripotent stem cells and differentiating them into disease resembling cells. CRISPR/Cas9 was used in modification of iPSCs to create or improve the disease model including muscle dystrophies, heart disease and Parkinson's disease. Combining iPSCs and CRISPR/Cas9 technology give significant result in understanding the disease and its cure [4].

Challenges and it's Solution

Although various advantages were discussed in various literatures, there is some challenges and limitation of CRISPR/Cas9 system which include methods of delivery, off-target cutting and ethical issues in human germline mutation [2]. Germino-Watnick, et al. [5] discussed that autologus hemopoetic stem cell targeted gene therapy gave one time potential cure of genetic hematological diseases with point mutation as in sickle cell disease and β thalassemia. They highlighted that CRISPR/Cas9, derived from the immune system of "Streptococcus pyogenes", was more efficient and easier to design which involved the single gRNA which target the DNA sequence. Editing required a protospacer adjacent motif (PAM) near the target. CRISPR/Cas9 faced challenges like off-target effects, genomic instability, and pre-existing antibodies to Cas9. CRISPR/Cas9 was preferred for its higher editing efficiencies and ease of use. It combined gRNA, Cas9 endonuclease, and donor DNA with homology arms. Delivery was mainly through electroporation for ex vivo and viral vectors or nanoparticles for in vivo applications. Various other Studies had shown varied success rates in gene modification and engraftment efficiency, highlighting the need for further optimization. At least 20% gene correction was required to reverse the sickle phenotype. Despite imperfections, clinical trials are ongoing [5].

Conclusion

The advent of CRISPR/Cas9 gene editing technology marked a revolution in advancement in genetic engineering, offering immense potential to correct genetic mutations at their source. Leveraged the bacterial immune system to precisely target and modify DNA sequences. The versatile applications of CRISPR/Cas9 in treating genetic disorders like sickle cell anemia and β-thalassemia. Despite its promise, CRISPR/Cas9 faced significant challenges, including off-target effects, genomic instability, and ethical concerns related to human germ line editing. The method of delivery remained a critical factor influencing editing efficiency and safety. Electroporation, viral vectors, and nanoparticles each offered a distinct advantages and limitations, necessitating further researches to refine and optimize. While CRISPR/Cas9 technology presents transformative possibilities in genetic medicine, addressing its technical and ethical challenges is crucial for realizing its full potential. Ongoing studies and clinical trials will continue to refine this powerful tool, bringing us closer to effective and safe gene therapies for a range of genetic diseases.

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