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Gene Therapy Shows Promise Against Sickle – Cell Disease

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ABSTRACT

Sickle Cell Disease (SCD) is a genetic blood disorder which is characterized by presence of abnormal hemoglobin (HbS) allele along with a second allele that can cause polymerization of such abnormal molecule. The state arises due to a genetic mutation that distorts red blood cells into sickle shaped. Sickle cells block red blood cells from passing through the blood vessels and prevent the supply of oxygen that results into severe complications like anemia, hypertension and organ failure.

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Treatment of sickle cell diseases includes gene therapy, cell transplantation. Gene Therapy focuses on the genetic modification of the cells to produce a therapeutic effect. Gene therapy holds a great promise in future of medical treatment. Gene Therapy itself comprises of multiple approach like gene addition, gene replacement and gene repair or chimeroplasty. Neonatal with SCD shows presence of healthy red blood cells due to fetal hemoglobin. Fetal hemoglobin refers to oxygen carrier in human fetus that also prevents cells to sickle. Post birth, the production of the fetal hemoglobin is inhibited due to the expression of the gene BCL11A gene that initiates the production of adult hemoglobin in the juvenile. BCL11A gene is a factor that can subdue expression of γ-globin in the erythroid cells. The genetic mutation causing the sickle cell disease is seen on the adult hemoglobin gene and not in the fetal hemoglobin. Gene Therapy in the sickle cell disease exhibits the effect by knocking down the expression of the gene BCL11A, which switches back the production of fetal hemoglobin . This gene therapy if successful can help correct the abnormal gene in SCD permanently. This will sidestep the problem associated with graft versus host rejection during bone marrow or stem cell transplantation. Lentiviral – mediated gene transfer has been used in mice to correct hematological defects. Lentiviral mediated gene therapy was used first against human for SCD by integrating normal beta globin gene into patient's hematopoietic cells.

Similar to gene addition using lentiviral vector, gene editing is also a promising area for treatment of genetic diseases. Ih helps correct a specific defective DNA sequence in its native location. It is a technique considered to be precise in genetically correcting a single base mutation in patient suffering from SCD. The treatment makes use of ZFNs along with CRISPR-Cas9 technology. CRISPR-Cas9 technology is also being explored to mimic the rare, genetic variants that promote expression of the γ-globin genes as in hereditary persistence of fetal haemoglobin [1,2]. The ultimate challenge, however, is to genetically correct the mutation, a single nucleotide change in the codon of the globin gene from GAG to GTG, by providing a homology template with the correct sequence at the sixth codon. Although this has been completed in preclinical studies, current techniques do not allow for specific transversion mutations like those required to cure SCD in humans [1,3]. Stem cell transplantation and gene therapy seem likely to become more applicable.

Over past 30 years, there have been tremendous advances in the medical sciences. Many advances has been made these years in understanding that pathophysiology and after effects of SCDans treatments in this area. The study shows a hope for translating these insights into better therapeutic options, that evolved inclusion of Pharmacogenomics to treat genetics related diseases.

Though no controlled trials of gene therapy have been found for sickle cell disease. The primary outcome of gene therapy should be a firm cure against SCD. The current viral vectors should be used with caution in humans. Gene Therapy being a promising field assures trials in the near future. But apart from gene addition, other methods like; gene editing, targeting HbS polymerization, targeting vasocculation, targeting inflammation can assist in curing Sickle cell disease.

Narrative

Sickle Cell Disease is a genetic, multisystem blood disorder which is caused due to the abnormalities seen in the haemoglobin molecule in which glutamic acid at position 6 of the β-globin chain of haemoglobin is changed to valine. Showed that this amino acid substitution arose from a single base change (A>T) at codon 6 (rs334).The abnormalities seen in the HbS allele is dur to the polymerization caused in the molecule. The polymerization is the genetic mutation that results in the distortion of the red blood cells making the cells undergo a sickle shaped which can prevent blood flow thereby creating anemic conditions in the patient.

Treatment of the Sickle cell disease includes various medications focusing on increasing hydroxyurea, use of L-glutamine for reduction of pain, voxelotor a drug to treat anemia. Similarly blood transfusion and bone marrow transplant are also seen as an effective treatment used against SCD. Stem cell transplant (bone marrow transplant) this procedure infuses healthy cells called stem cells, into the body to replace damaged or diseased bone marrow (bone marrow is the center of the bone where blood cells are made) (CDC) .

Sickle cell disease is a autosomal recessive disease becomes a good candidate for gene therapy which can help restore a normal phenotype into diseased cells with a single normal copy of mutant gene. Gene Therapy is genetic modification of the cells producing a therapeutic effect. Gene therapy in sickle cell works by knocking down the expression of the BCL11A gene to flip the switch back to fetal hemoglobin, simultaneously increasing fetal hemoglobin, which does not sickle, and directly reducing sickling hemoglobin. To perform gene therapy, a patient's blood stem cells are collected and exposed to a vector containing instructions to knock down BCL11A. The patient then receives chemotherapy in a process called conditioning, likened to plowing a field to make room for new seeds. Finally, the gene-modified cells are given back via intravenous infusion. According to a research[2]. Genetic disorders group haemoglobinopathies trials were performed and it was found that no trials for gene therapy against Sickle cell disease were found effective.

Other than this; patients undergoing autologous stem cell transplant requires collection of hematopoetic stem cells (CD34+). The harvesting of these cells can be done by bone marrow harvest or a alternative approach using Plerixafor . Plerixafor acts by reversibly blocking the binding between chemokine CXC-receptor 4 (CXCR4). It induces peripheral mobilization of stem cells by releasing CD34+ cells from bone marrow niches.
Gene addition using lentiviral vector are profoundly used to carry therapeutic genes. In gene addition patient's stem cells are infected with lentivirus expressing a beta globin variant. This method is called anti-sickling gene therapy. Other gene addition method makes use of Hb F induction that makes use of lentiviral mediated erythroid specific short hair-pin RNA that targets the specific gene and down regulates it's expression. Viral vectors, such as lentivirus, are a great tool for gene therapy.

Apart from gene addition, gene editing is a important tool for treatment of SCD . Gene editing corrects a specific DNA at a particular sequence in a segment. SCD presents a attractive prototype . The strategies included in gene editing includes ZFNs , TALENs and use of CRISPR associated nucleases Cas-9 techniques . The CRISPR – Cas9 technology involves forming double stranded break (DSB) in the targeted sequence with assistance of a guide RNA . One of the common methods of repair of a DSB involves non-homologous end joining resulting into gene disruption . This strategy is currently being tested in a clinical trial (ClinicalTrials. gov Identifier: NCT03745287) in which the patient's own BCL11A gene (a major inhibitor of γ-globin gene expression) is disrupted to induce HbF expression. BCL11A also has roles in lymphoid and neurological development but gene-editing for SCD exploits the erythroid-specific enhancers in intron 2 of the gene.

The clustered regularly interspaced short palindromic repeats (CRISPR) associated with a nuclease system Cas 9 which is a bacterial immune system that can cleave Bacteriophage or a plasmid DNA targeting insertions and deletions at a specific site of the genomic DNA. Guide RNA attaches to a specific target DNA site at one end while other end binded with the Cas 9 enzyme. Here CRISPR - Cas9 gene editing techniques is used in hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of BCL11A to reduce BCL11A expression in erythroid-lineage cells, restore γ-globin synthesis, and reactivate production of fetal hemoglobin.

In the paper published in the New England Journal of Medicine, CRISPR-Cas9 Gene Editing for Sickle Cell Disease and beta-Thalassemia, researchers reported gene editing modified the DNA of stem cells by deleting the gene BCL11A, the gene responsible for suppressing fetal hemoglobin production. This approach shows advantage that it makes use of patients cells without having a donor. Also the gene manipulation does not require a viral vector. The goal of CRISPR technology is to delete mutations concerned with disorders. However in-vivo effects of CRISPR-CAS9 have not been looked upon. There are open clinical trials in United States for CRISPR for a potential treatment against SCD. CRISPR approach of gene editing has been a promising tool against such genetic disorders.

Conclusion

SCD is a blood disorder that was characterized more than before a century. Yet definitive treatment for every patient is not available. There has been a major revolution in the field of medical sciences that tremendous progress has made is easier to understand the pathophysiology of the disease and to come up with a promising alternative as a aid . After a century, going back to the basics tends to offer better therapeutic options. The CRISPR-Cas9 editing of BCL11A in hematopoetic stem cells with high levels of fetal hemoglobin expression while eliminating need for transfusion. CRISPR-Cas9 is cost effective, easily applicable. Studies show that CRISPR technology can be effectively used to treat the SCD mutations. Concerns still arise considering tthe safety dut to random off-target effect. Focus should be made on conducting trials over large animal models considering the safety approach.

Clinical trials of CRISPR-CAS9 with SCD investigating the prospective are still in progress. This approach will certainly direct the approach of treatment. The application is definitely promising but currently not feasible to undertake in routine especially in less developed countries like Africa with great prevalence of the disease. Along with this production of cost effective RNA and Cas9 should be implemented to increase the use. The promise of gene therapy as a cure for SCD is becoming a reality, questions and challenges do prevail to ensure that this approach is feasible, safe and a permanent curative measure in the future of medicines.

References

1. Haydar Frangoul, David Altshuler, M Domenica Cappellini, Yi-Shan Chen, Jennifer Domm, et al. (2021) CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia 384: 252-260.
2. Abiola Olowoyeye, Charles I Okwundu (2018) Gene therapy for sickle cell disease 11.
3. Selami Demirci, Alexis Leonard, Juan J Haro-Mora , Naoya Uchida , John F Tisdale et al. (2019) CRISPR/Cas9 for Sickle Cell Disease: Applications, Future Possibilities, and Challenges 1144: 37-52.