CRISPR-Cas9 AND ITS APPLICATION AS A GENE-EDITING STRATEGY FOR β-HEMOGLOBINOPATHIES: A LITERATURE REVIEW

Sukhmani Ashok[1]

[1]*Caucasus International University, School of Medicine, Tbilisi, Georgia.*

Giorgi Dugashvili[2]

[2]*Grigol Robakidze University, School of Medicine, Tbilisi, Georgia.*

ABSTRACT

The purpose of this literature review is to discuss the gene editing strategy of clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR-Cas9) for β-hemoglobinopathies. With approximately 100,000 individuals affected by sickle cell anemia (SCA) in the United States and millions worldwide, the discovery of CRISPR-Cas9, has been one of the most prominent advances of the 21st century. It is a gene-editing tool, a technology that allows scientists to alter an organism's DNA, that was discovered as a part of the adaptive immune system of archaea and bacteria as they defend against plasmids and phages.

Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 is an advanced alternative to other gene-altering technologies resembling transcription activator-like effector nucleases (TALEN) and zinc-finger nucleases (ZFN). Attributed to its great efficiency and precision, CRISPR has been found to have many applications in the field ranging from the treatment of cancer to even β-hemoglobinopathies. Despite having a high prevalence rate and a chronic crippling nature, β-hemoglobinopathies are a group of monogenic diseases that have only a few therapeutic options available.

With the advancement in genome editing therapeutic strategies, a few clinical trials are in progress studying CRISPR-based treatments in Sickle cell anemia and β-thalassemia patients. Three patients who were treated with the therapy, two with transfusion-dependent β-thalassemia and one with SCA have discontinued RBC transfusions.

While CRISPR-Cas9 provides easy genome editing with several benefits, the ethical and biosafety issues cannot be ignored. Furthermore, any tool with such potential carries a risk of being unlawfully used for non-legal purposes. With the ever-growing developmental strides in the CRISPR-Cas9 technology, it may not only widen the scope of treatment options for β-hemoglobinopathies but to even envision a cure.

Keywords: CRISPR, gene editing, sickle cell anemia, hemoglobinopathy, genome engineering, thalassemia.

Introduction

Hemoglobin is a Heterotetramer meaning it comprises of four globin chains: adult hemoglobin (Hb A) has two α and two β chains (α2β2) and fetal hemoglobin (Hb F) has two α and two gamma chains (α2γ2). These chains transport oxygen throughout the body. β-hemoglobinopathies are a set of diseases that are distinguished by the qualitative or the quantitative defects in β-globin synthesis. Qualitative defects, such as in the case of Sickle Cell Anemia, emerge from the mutations in the HBB gene (which encodes β-globin) giving rise to an altered β-globin molecule. Sickle Hb (HbS) is a structural variant of the adult Hb (HbA) that is caused by a single nucleotide change from A-to-T transversion in the 6th codon of the HBB gene, substituting hydrophilic glutamic acid with a hydrophobic valine, i.e, a p.Glu6Val substitution. Any β-hemoglobinopathy which contains the HbS allele falls under the term Sickle cell disease (SCD) (Modell, 2008). Sickle Cell Anemia (SCA) is the most severe type of SCD that results from the homozygosity of the HbS allele. There are two more common structural variants of the β-globin chains, HbC (Nagel, Fabry, & Steinberg, 2003) and HbE (Orkin et al., 1982). Homozygosity of