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CRISPR-MEDIATED THERAPEUTICS: I. NEURODEGENERATIVE DISEASES

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Abstract:

Neurodegenerative disorders are a group of disorders that affect elderly, with a small portion being hereditary in nature. Both genetic and non-genetic factors contribute in the development of this array of diseases. With the majority of cases being sporadic, the search for authenticated therapeutic option is demanding. Recently, CRISPR/Cas9-based therapy become potential to treat several human diseases, especially neurodegenerative such as Parkinson disease (PD), Huntington disease (HD), Alzheimer disease (AD), and amyotrophic lateral sclerosis (ALS). In this minireview, we highlight how CRISPR/Cas9 become in action to treat these life-threatening diseases and widen the view to the future perspectives and limitations of this technology towards other complicated diseases such as frontotemporal dementia (FTD) and the spinocerebellar ataxias (SCA).

Key words: *CRISPR; Parkinson; Huntington; Alzheimer; amyotrophic lateral sclerosis.*

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INTRODUCTION:

CRISPR/Cas9 is powerful yet simple tool designed for editing almost all genomes [1] (Fig. 1).

This technology has been discovered in bacteria and archaea as a means of immune defense mechanism [2]. CRISPR allows researchers to easily and straightforwardly insert, delete, correct genes within the organism' genome [3]. Being new technology, a bunch of ethical concern were raised, trying to control the misuse of this potent weapon.

Up until the moment, there are no curative treatments for neurodegenerative disorders such as PD, HD, AD, and ALS [4-6]. This array of diseases is characterized by late onset as it appears normally in elderly people with minor cases affect younger ages [7]. The majority of these diseases are sporadic in nature, meaning that the genetic intervention is quite limited [8]. Nonetheless, this obstacle might narrow the therapeutic scope, leaving patients with no curative treatment. CRISPR/Cas9-based approaches to treat neurodegenerative disorders are under progress and might be available in clinics very soon (Fig. 2).

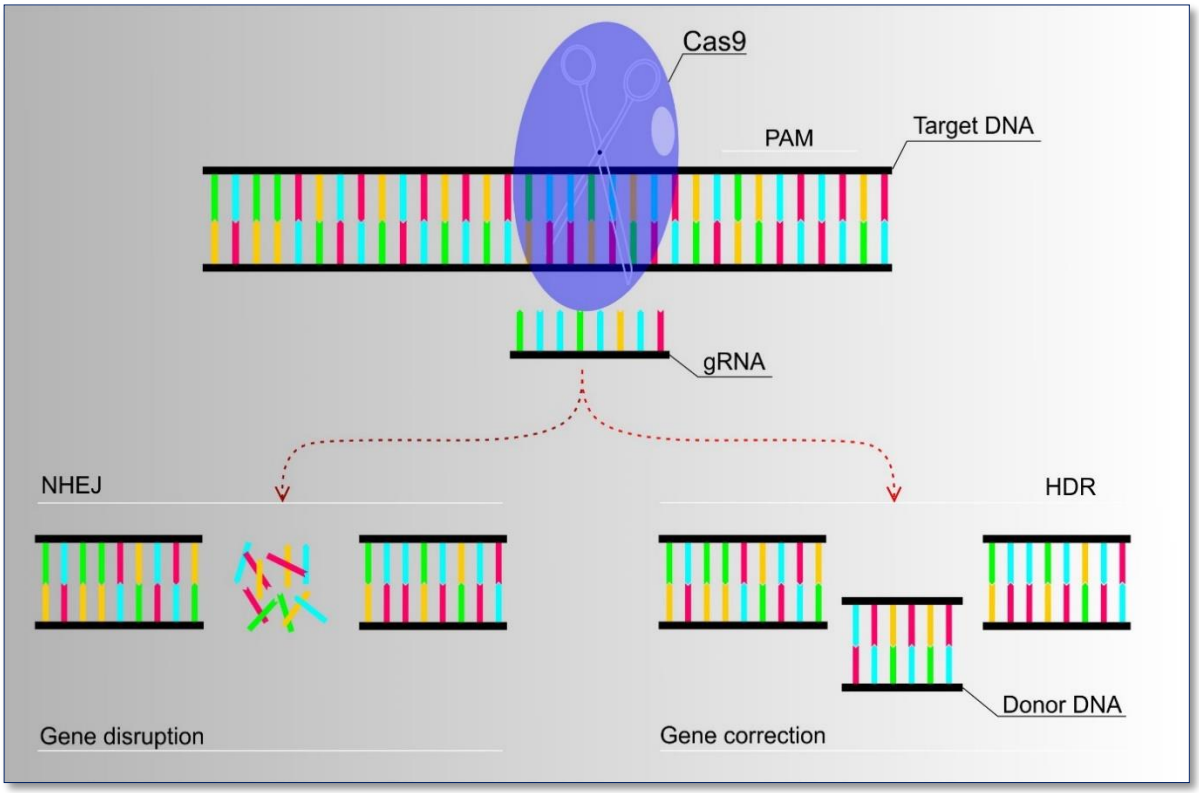

Figure 1. Schematic representation of CRISPR mechanism. NHEJ; Non-homology end joining, HDR; Homology-directed repair, PAM; Protospacer adjacent motif.

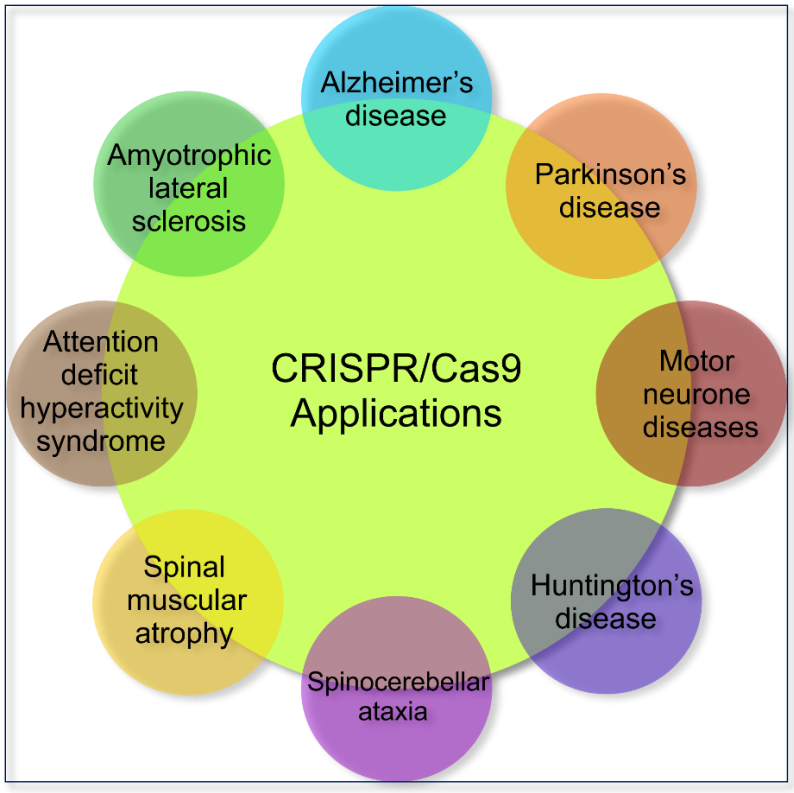

Figure 2. CRISPR/Cas9 related neurodegenerative disorders.

Huntington's disease

HD is caused by a mutation in the *HTT* gene (encoding huntingtin), where heterozygous nullifying results in severe neurodevelopmental disorder [9]. The genetic nature of this disease enables CRISPR/Cas9-mediated silencing of the mutant allele. Recent advancement in CRISPR-based HD treatment took place using SNP-based elimination of PAM sequence. A mutant allele-specific guide RNA (gRNA) was designed to target *HTT* promoter region and the CAG repeats in the exon 1. In patient-derived iPS cells, this approach was successful in deleting a DNA long stretches including the promoter sequence of the mutant allele without disrupting the normal *HTT* allele [10-12].

Alzheimer's disease

AD is a progressive neurodegenerative disorder, which is considered a common cause of human dementia with high outbreak rates, where about 65 million people could suffer from AD by 2030 worldwide [13-15]. Several approaches utilizing CRISPR technology to combat AD has been introduced. Most recently, Sun, Carlson-Stevermer [16] used CRISPR/Cas9 to edit the amyloid precursor protein (*APP*) gene aiming to attenuate β-cleavage and amyloid-β (Aβ) formation, and upregulating the neuroprotective α-cleavage process. By editing *APP* and hence disrupting the β cleavage, the Aβ –the AD-causing protein- will not be accumulated, allowing the cells to behave normally.

Parkinson's disease

PD is a severe neurodegenerative disease, with some cases are caused by an autosomal dominant mutation in the alpha-synuclein *(SNCA)* gene. Mutations in *SNCA* causes accumulation of Lewy bodies and Lewy neurites, leaving patients suffer from early onset PD. In the course of editing the faulty gene that cause PD, Basu, Adams [17] used CRISPR/Cas9 in patient-derived stem cells to edit *SNCA* through targeting multiple exons, and the results were validated in HEK293 cells *in vitro.*

Amyotrophic lateral sclerosis

ALS (aka Lou Gehrig's disease) is a fatal, yet rare neurodegenerative disorder, where the neurons responsible for controlling muscle movement were affected, leading to progressive muscle weakness. Mutations in super oxide dismutase (SOD1) is associated with 20% of the inherited forms of ALS. The normal function of this protein is to convert

superoxide anions into hydrogen peroxide, making it crucial to the cell's antioxidant defense mechanism. Recent studies indicated the utilization of CRISPR/Cas9 to disrupt the faulty version of SOD1 in mice with ALS. This approach was successful in extending the lifespan of mice by 25%, making it possible for future applications on human [13, 15, 18].

Limitations and future directions

Although the ease of use and the straightforwardness of CRISPR technology, there have been some limitations that should be taken into consideration [19]. The major hurdle is off targeting, which might lead to unpredictable/undesired mutations [20]. Furthermore, using viral vectors such as adenoviral vectors (AV) or Lentiviral (LV) is associated with lower cargo capacity and tissue tropism along with the potential conversion to the virulence state, which limits their uses. Using non-viral delivery method such as electroporation microinjection, and lipofection is safer for the time being [21].

Other neurodegenerative disease such as FTD and SCA are among the hot areas of CRISPR research aiming to eradicate these diseases *via* hitting the faulty, disease-causing genes.

In conclusion, CRISPR/Cas9-based therapies bear strong potentialities to treat several life-threatening diseases including neurodegenerative disorders such as AD, PD, HD, and ALS.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contribute equally.

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