Extended Abstract Journal of Clinical & Experimental Toxicology 2021
Vol.5 No.1

OSKM Mediated Delay In Ageing Clock: CRISPR Cas 9 Approach- Akanksha Singh - RTMNU

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Abstract

Ageing is a consequence of several changes in the epigenome that ultimately results in decreased functionality in tissues as well as organs. Hence, it is crucial to re-build the functioning pattern of the aged cells by acquiring pluripotency. OSKM (OCT 4, SOX 2, KLF 4, MYC) pathway is known to re- create pluripotency in aged cells by various mechanisms. This group of transcription factors can be targeted for specific inhibitory pathways like oxidative stress and inflammation promoting molecular aging. This study aims to probe the molecular crosstalk among the four transcription factors with the CRISPR Cas 9 approach that will prevent the transfer of aged genome to the offspring. The activators associated with CRISPR Cas were exposed to four transcription factors. Yamanka factors were introduced in mouse model in vivo along with CRISPR genes showed the possibility of editing the inhibitory genes. With advances in medical technology, the number of people over the age of 60 is on the rise, and thus, increasing the prevalence of age-related pathologies within the aging population. Neurodegenerative disorders, cancers, metabolic and inflammatory diseases are some of the most prevalent age-related pathologies affecting the growing population. It is imperative that a new treatment to combat these pathologies be developed. Although, still in its infancy, the CRISPR-Cas9 system has become a potent gene-editing tool capable of correcting gene-mediated age-related pathology, and therefore ameliorating or eliminating disease symptoms. Deleting target genes using the CRISPR-Cas9 system or correcting for gene mutations may ameliorate many different neurodegenerative disorders detected in the aging population. Cancer cells targeted by the CRISPR-Cas9 system may result in an increased sensitivity to chemotherapeutics, lower proliferation, and higher cancer cell death. Finally, reducing gene targeting inflammatory molecules production through microRNA knockout holds promise as a therapeutic strategy for both arthritis and inflammation. Here we present a review based on how the expanding world of genome editing can be applied to disorders and diseases affecting the aging population. Current genome-editing systems generally rely on inducing DNA double-strand breaks (DSBs).

This may limit their utility in clinical therapies, as unwanted mutations caused by DSBs can have deleterious effects. CRISPR/Cas9 system has recently been repurposed to enable target gene activation, allowing regulation of endogenous gene expression without creating DSBs. However, in vivo implementation of this gain-of-function system has proven difficult. Here, we report a robust system for in vivo activation of endogenous target genes through trans-epigenetic remodeling. The system relies on recruitment of Cas9 and transcriptional activation complexes to target loci by modified single guide RNAs. As proof-of-concept, we used this technology to treat mouse models of diabetes, muscular dystrophy, and acute kidney disease. Results demonstrate that CRISPR/Cas9-mediated target gene activation can be achieved in vivo, leading to measurable phenotypes and amelioration of disease symptoms. This establishes new avenues for developing targeted epigenetic therapies against human diseases.

Throughout the world, people over 60 years of age are becoming an increasingly large percentage of the total population. In the year 2012, the estimated population over the age of 60 was about 43.1 million or less than 20% of the U.S. population. However, the projected number of the American population reaching the age of 60 and older by the year 2050, is expected to reach around 83 million or about 25 - 30% of the U.S. population. This information is

according to the U.S. Census Bureau .With the increase in human life expectancy comes an increase in the prevalence of age-related pathologies and health burdens in the aging population .Neurodegenerative disorders, cancer, metabolic and inflammatory diseases are some of the most prevalent age-related pathologies affecting this growing population]. In this new era of targeting therapeutics, gene editing promising tool against a plethora of diseasesIn tiis a promising tool against a plethora of diseases .The most imperative and critical requirement to understand the pathological mechanisms of the diseases is understanding the functions of a gene or multiple genes in primary human cells and targeting them.

Since it was first discovered in *Caenorhabditis elegans*, RNA interference (RNAi) was used as a mechanism to knockdown genes of interest . However, this technology presents multiple drawbacks, including incomplete or insufficient knockout and off-target effects . The clustered regularly interspaced palindromic repeats- (CRISPR-) associated (Cas) protein 9 (known as CRISPR-Cas9) system targets and induces site-specific DNA double-strand breaks (DSBs) directed by a single-guide RNA (sgRNA) that enables the editing of the genome by adding, removing, or altering sections of the DNA sequences in a variety of species . The concept of ene-editing by a complete knockout of a gene in human cells with minimal off-targeting events represents a powerful approach to study gene function and to discern the molecular mechanisms underlying complex human diseases with the ultimate goal of improving the quality of gene therapy studies . This method has been employed to identify or investigate: cancer-associated gene function, revealing the role of numerous variants and the non-coding region in tumor development, epigenetic mechanisms, cancer risk via a genetic screen, the development of animal models, and as a potential cancer therapeutic tool . There are three types of CRISPR-Cas9 gene editing systems . The most studied system is the Type II, that was adapted from a naturally occurring genome editing system in the bacteria *Streptococcus pyogenes* . Here we will briefly discuss the different forms of the CRISPR-Cas9 technology. However, an in-depth review of CRISPR-Cas9 cell entry and mechanism of action is beyond the scope of this review and already covered in great detail elsewhere.