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Implications of Genome Editing Technology in Human Disease Targeted Therapy

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Editorial

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DESCRIPTION

Genome editing technologies, which are based on manmade or bacterial nucleases, have opened up the possibility of directly targeting and changing genomic sequences in practically all eukaryotic cells. Genome editing has increased our ability to understand the role of genetics in disease by facilitating the development of more accurate cellular and animal models of pathological processes and it has begun to show extraordinary promise in a wide range of fields, from basic research to applied biotechnology and biomedical research. Recent advancements in the development of programmable nucleases, such as Zinc-Finger Nucleases (ZFNs).

The invention of genetic engineering (DNA or RNA modification) in the 1970s ushered in a new era in genome editing. Genome editing methods, which are based on manmade or bacterial nucleases, have advanced rapidly in the last ten years and have begun to show amazing applicability in a variety of domains, spanning from fundamental research to applied biotechnology and biomedical research. 2 Genome editing can be done *in vitro* or *in vivo* by delivering the editing machinery *in situ*, which can powerfully add, ablate and "fix" genes, as well as make other highly targeted genomic modifications. The production of nuclease-induced Double-Stranded Breaks (DSBs) leads to the stimulation of very effective cellular DNA recombination processes in mammalian cells, which leads to targeted DNA changes. In practically all cell types and organisms, nuclease-induced DNA DSBs can be repaired by one of two basic mechanisms. Homology Directed Repair (HDR) or Non-homologous End-Joining (NHEJ), resulting in targeted integration or gene disruptions. Historically, Homologous Recombination (HR), which uses undamaged homologous DNA pieces as templates to achieve targeted gene addition, replacement, or inactivation, has been the method of choice. However, HR's effectiveness in mammalian cells and model animals has been severely constrained. Targeted nucleases have been developed as an alternate strategy to increasing the efficacy of HDR-mediated genetic modification when it was recognized that DSBs could increase the incidence of HDR by numerous orders of magnitude. HDR can reconstruct the cleaved DNA using an exogenous DNA template homologous to the break site sequence once a specific DSB has been produced. By directly introducing an adequately designed repair template into targeted cells, this process might be exploited to create exact alterations. As a result, mutation repair or novel sequence insertion occurs in a site-specific way. NHEJ-mediated repair, on the other hand, is prone to mistakes because it results in the effective production of gene insertion or deletion (indels) of various lengths at the

DSB site, eventually leading to gene inactivation. If indels exist in the coding sequence, frame shift mutations occur, resulting in mRNA degradation or the generation of non-functional truncated proteins *via* nonsense-mediated decay. Because there is no need for a repair matrix and the cell type has less impact on modification efficacy, this technology, and its applications are anticipated to be easier than HR-based methods (contrary to HR, NHEJ may be active all through the cell cycle). NHEJ can be used to inactivate a single or several genes in immortalized cell lines, but by causing loss-of-function mutations, it results in irreversible gene inactivation. The engineering of unique Zinc-Finger Nucleases (ZFNs) or mega nucleases has been the focus of study in the early stages of genome editing to induce the desired DSBs at specific DNA target sites. These nuclease systems necessitated specialized expertise to create artificial proteins made up of sequence-specific DNA-binding domains coupled to a nonspecific nuclease for target cleavage, giving researcher's unparalleled access to genetic manipulation tools. Following that, the discovery of a new class of *Flavobacterium okeanokoites* (FokI) catalytic domains generated from bacterial proteins known as Transcription Activator-Like Effectors (TALEs) has opened up new avenues for precise genome editing. TALE-based programmable nucleases have a high frequency of cleavage of any DNA sequence of interest. The construction of a sophisticated molecular clone for each novel DNA target, as well as the low effectiveness of genome screening in successfully targeted cells, is the key hurdles for Transcription Activator-Like Effector Nucleases (TALEN) techniques. The clustered regularly interspaced short palindromic repeat (CRISPR)-associated 9 (Cas9) nuclease, which is developed from a bacterial adaptive immune defense system, is a powerful gene-editing tool. It has emerged as a viable alternative to ZFNs and TALENs for inducing targeted genetic alterations since it can be efficiently programmed to edit the genome of eukaryotic cells *via* an RNA-guided DNA cleavage module. The versatile CRISPR/Cas9 technology has been quickly increasing its usage in modifying gene expression, spanning from genomic sequence repair or change to epigenetic and transcriptional modifications, since it was initially introduced in mammalian cells as a tool to edit the genome.