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# Does Genome Editing Have Clinical Implication?

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## Mini Review

Genome editing by definition is a type of engineering to change the nucleotides in the genome of a living organism through insertion, deletion or mutation process. The process can be accomplished by a number of nucleases. The editing is carried out by DNA repairing process. These nucleases either nick or cut the double-stranded DNA. Earlier work of genome editing involves zinc finger nuclease [1]. Due to the problem of specificity and the limit of target sequences, it is difficult to apply the zinc finger nuclease robustly to genome editing. In 2009, transcription activator-like effector nuclease (TALEN) was introduced as a new genome-editing tool. It offers a larger range of target sites [2,3]. In theory, TALEN can be used to target any genome sequence. Thus, it offers potential for a wide variety of application for genome editing. Currently, most of TALEN genome editing has been applied to plant genome editing. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) was originally discovered as one of the immunity defense mechanisms against foreign pathogens in prokaryotic cells [4]. Cas9, a critical protein for type II of CRISPR/Cas system, was found to contain DNA cleavage activity. The nuclease activity of Cas9 was guided by 20 bases complementary sequence from CRISPR RNA and trans-activating CRISPR RNA to the targeted DNA [5]. Since trans-activating CRISPR RNA and CRISPR RNA can be made into a chimeric RNA containing the full function of both RNA species, guide RNA (gRNA) was coined for the artificial fusion RNA [6]. The advantage of CRISPR-cas9 editing system is its robust cleavage of targeted DNA, and the ease of creating new editing constructs in relatively non-expensive way. D10A mutation in the catalytic domain of Cas9 converts it to nickase that produces single nucleotide break at the target DNA [5]. Double nicking of target DNA increased genome editing specificity by 50-1500 fold [7], with the off-target rate as low as 1/10,000. Such specificity makes somatic genomic targeting a viable approach in treating human diseases. More recent advance of gene editing extends to adenine base editor without DNA cleavage by fusing adenine deaminase into catalytically inactive Cas9 [8]. Such system appears to be efficient due to the high efficiency of the deaminase.

The potential clinical application of genome editing to treat human diseases is very tantalizing. Correction of germline mutations of human hereditary diseases is the obvious application. Correction or creation of mutation has been successful in animal models. In the US and Europe, clinical trials have been planned on several human diseases. Most notably, a gene-editingphase I/II trialis planned in Europe for human β-thalassemia in 2018, and a subsequent trial for sickle cell anemia in the US. This therapeutics is planned as *ex vivo:* The hematopoietic cells are edited outside the human bodies. These cells are then re-introduced into the same patients after the mutations are corrected. *Ex vivo* approach has also been used to treat an array of human cancers in China: The immune T cells from cancer patients are edited to block the expression PD-1 (program cell death-1). These genetically modified T cells that are not inhibited by cancer inhibitory ligand are infused into the same patients' bodies to induce animmune response to combat the cancer cells. The initial results from such approach appear mixed. Recently, the genome editing technology has been modified to target at the chromosome rearrangement in cancer cells [9]. Many cancer specific chromosome rearrangements produce fusion genes [10,11]. Since these chromosome rearrangements occur only in cancer cells but not normal cells, the effect of cancer-killing appears highly cancer specific. Such approach has been very successful in the mouse models.

The roadblocks remain for the efficient application of genome editing therapy to ahuman being. One of the main challenges is the presence of antibodies for Cas9 in a significant portion of human population [12]. However, it is unclear whether these antibodies can neutralize the protein. Since Cas9 is localized in the nucleus of the cells, it remains to be seen whether these antibodies interact with the antigen in vivo. Off-target is another potential issue for the application of genome editing system in human. Even if the off-target rate is relatively low, it is unclear what the long-term impact is. Only extensive application of genome editing to treat human diseases will tell.

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