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LETTER TO THE EDITOR

Zinc-finger Nucleases and Their Application in the Treatment of Genetic Diseases

Zinc-finger nucleases (ZFNs) are DNA-binding proteins coupled to the catalytic domain from the FokI restriction endonuclease.[1] ZFNs create double-strand breaks in specific DNA sequences, stimulating the cell's endogenous DNA repair processes.[2] They can also be engineered to target a desired DNA sequence allowing a site-specific manipulation of the mammalian genome in a wide variety of cells, resulting in cell lines with targeted gene modification. For a long time, ZFN technology has been looked upon by researchers in the treatment of inherited genetic mutations. Functionally corrected patient-derived stem cells can be used for autologous transplantation therapies and to cure various diseases.[3]

Recently, engineered ZFNs have been employed successfully to manipulate the human genome of induced pluripotent stem cells derived from sickle cell anemia and X-linked chronic granulomatous disease patients.[4] In addition, Phase 1 clinical trials employing ZFNs to treat glioblastoma and human immunodeficiency virus (HIV)/AIDS are under way. The C-C chemokine receptor type 5 (CCR5) protein on T-cells, required by certain HIV viruses to enter and infect these cells, may become resistant due to ZFN-mediated introduction of mutated CCR5 alleles. This technology can also be used to treat a wide variety of hemoglobinopathies, as successful correction of α-thalassemia has already been reported.[5]

In spite of successful clinical trials, ZFN-mediated gene therapy has still not been completely put into clinical practice due to unclear challenges. ZFN-induced genotoxicity and cytotoxicity are among the major issues that need to be resolved prior to the full implementation of their clinical application. The introduction of genomic double-strand breaks has been shown to induce cell cycle arrest and cell death, apart from triggering multiple DNA damage response pathways and altering the activity of numerous cellular proteins.[2] Furthermore, illegitimate integration and off target DNA modification have still not been fully understood and needs further research. Finally, there is also a need to develop both safer ZFNs and safer delivery methods to minimize genotoxic side effects. However, in view of the progress made in the past decade, one cannot help but feel optimistic about the revolution ZFN technology can bring in the field of medicine.

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