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Gene Technology

Commentary

Incorporating Genetic Engineering Techniques in Human Gene Therapy

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DESCRIPTION

Gene therapy is a therapeutic approach that employs genetic engineering methods to treat different ailments. Gene therapy first advanced with the creation of recombinant DNA in the early 1960s and was further developed utilising a variety of genetic engineering methods, such as viral vectors. Genome editing tools, such as Zinc-Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and the more modern clustered regularly interspaced palindromic repeats/CRISPR-associated-9 (CRISPR/Cas9) technologies, was created in the 2000s. These tools cause mutations to the genome at predetermined target regions [1]. Genome editing technologies are effective for deliberate genetic engineering, which has prompted the development of novel therapeutic approaches for a variety of ailments, including cancer and hereditary diseases.

Development of viral vectors

Viral vectors remained essential ingredients in the creation of cell and gene therapy. Many hereditary illnesses, such as Leber's Congenital Amaurosis (LCA) and reverse Lipoprotein Lipase Deficiency (LPLD), were treated by Adeno-Associated Viral (AAV) vectors. 2008 saw the publication of impressive results from phase I/II clinical studies for LCA type II. Retinoid isomerase is encoded by the *RPE65* gene, which is highly expressed in the retinal pigment epithelium and causes the rare hereditary retinal degeneration disorder known as LCA. These tests show that *RPE65* could be delivered into retinal pigment epithelial cells using recombinant AAV2/2 vectors, leading to therapeutic advantages without unfavourable outcomes. For patients with LCA type II, the FDA has approved voretigene neparvovec-rzyl [2]. The first medication based on gene therapy to reverse LPLD was licenced in Europe in 2012 and is called Alipogene tiparvovec Glybera. The muscle cells receive an entire LPL gene from the AAV1 vector. AAV vectors have been used in more than 200 clinical trials for a number of hereditary disorders, including haemophilia, retinal dystrophy, and spinal muscular atrophy.

One of the cornerstones of gene therapy methods continues to be retrovirus. Strimvelis, an FDA-approved medication, is a gamma retrovirus-containing autologous CD34 (+)-enriched cell population that was employed as the first stem cell gene therapy in patients with SCID due to ADA deficiency. Retroviral vectors were thereafter frequently utilised for other genetic illnesses, such as X-SCID. Lentivirus is a member of a group of viruses that cause illnesses like acquired immunodeficiency syndrome, which is brought on by the human immunodeficiency virus (HIV), which infects cells by inserting DNA into the genome of its host cells [3]. The lentivirus has a larger range of possible applications because it may infect cells that aren't dividing. A lentiviral vector with a defective peroxisomal adenosine triphosphate binding cassette was used to treat individuals with X-linked adrenoleukodystrophy successfully.

Brain cancer gene therapy approaches

Tumor gene therapy differs from gene therapy for genetic illnesses, which involves inserting new genes into a patient's cells to replace any damaged or absent genes. The development of suicide gene therapy for malignant tumours was a breakthrough in gene therapy. Four individuals had anti-tumor activity after receiving stereotactic intratumoral injections of murine fibroblasts that produced a retrovirus vector with a suicide gene and a replication-deficient retrovirus vector. Different therapeutic gene types have since been employed to treat malignant glioma. Suicide genes for immunomodulatory cytokines and genes for reprogramming have been applied to the treatment of malignant glioma using viral vectors [4]. Recently, aggressive glioma was treated with a nonlytic, amphotropic Retroviral Replicating Vector (RRV) and immortalised human Neural Stem Cell (NSC) line. In the trial, there were no grave toxicities found. In general, it might be challenging to find NSCs made from human embryonic or foetal cells. Because it involves the death of human embryos, using human embryos for research on embryonic stem cells is morally dubious. Similarly, using foetal tissue obtained through abortion poses ethical questions. Organotypic brain slice culture has recently been used to demonstrate the tumor-trophic migratory activity of NSCs

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produced from human-induced pluripotent stem cells (hiPSCs). Additionally, hiPSC-derived NSCs with the HSV-TK suicide gene system showed significant therapeutic potential for treating experimental glioma models. Additionally, iPSCs can resolve NSCs' practical and ethical problems in therapeutic applications.

CRISPR/Cas9 and TALEN technologies have enhanced the effectiveness of cancer immunotherapy employing genome-engineered T cells in addition to these encouraging ongoing clinical trials for hereditary illnesses. Engineered T cells produce artificial receptors that can detect tumour cell epitopes. The FDA has approved two CD19-targeting CAR-T cell therapies for diffuse large B-cell lymphoma and B-cell acute lymphoblastic leukaemia. Many other blood cancer antigens are the focus of engineered CARs, including CD30 in Hodgkin lymphoma and CD33, CD123, and FLT3 in acute myeloid leukaemia. It has been demonstrated that PD-1 disruption caused by Cas9 in CAR-T cells enhanced the anti-tumor efficacy [5]. Through the optimization of various vector types and the introduction of new procedures, such as genome editing tools, gene therapy has advanced therapies for patients with cancer and congenital illnesses in recent decades. Because of its great effectiveness, low cost, and simplicity of usage, the CRISPR/Cas9 system is regarded as one of the most potent tools for genetic engineering. The development of CRISPR technology is ongoing and is anticipated to continue. These techniques provide the possibility of treatment for a wide range of human disorders, despite the fact that there are still many difficult challenges to overcome to achieve safe clinical application.

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