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Opinion Article

Gene Editing in the Field of Cancer Therapy

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DESCRIPTION

Cancer is one of the leading causes of death worldwide, and it continues to be a major social and economic burden. Individual genome mutations are becoming more common as a result of the rapid advancement of xenobiotics and industrialization in the modern world. With advances in molecular biology, it is now possible to alter the genome using gene-editing technology and study the functional changes resulting from genetic manipulation. Adoptive T-cell therapies have recently showed impressive signs of action, but technologies that raise T-cell potency while lowering the cost and labour associated in manufacturing these products could improve their clinical impact. In this field, gene editing platforms are being investigated to:

Improve immune cell potency by knocking out molecules that inhibit immune responses

Deliver genetic payloads into precise genomic locations, thereby improving safety and/or improving gene expression profile by leveraging physiologic promoters, enhancers, and repressors, and

Enable off-the-shelf therapies by preventing alloreactivity and immune rejection.

Adoptive T-cell therapies, such as Chimeric Antigen Receptor (CAR) T-cells, tumour-infiltrating lymphocytes, and T-cells modified to express Tumour-Specific T-cell Receptors (TCRs), can remove significant tumour burdens and provide long-term disease management, although most patients do not benefit. Adoptive T-cell treatments for cancer are very costly and time-consuming to produce, and autologous products have broad variations in potency due to inter-individual variability. Master cell banks of allogeneic products engineered to mediate antitumor effects, prevent Graft-Versus-Host Disease (GVHD), and avoid immune rejection, according to some, could be a significant advance because they could be multiplied for increased potency and manifest greater consistency at a lower cost. As a result, researchers are working hard to combine genetic engineering, synthetic biology, and gene editing to create more effective adoptive immune cell therapies that are more accessible and less expensive. Gene editing modifies cells' DNA in a site-specific manner. The ability to edit the genome of a mammalian cell was initially established by expressing an endonuclease in murine cells, which caused a double-strand DNA break that was repaired using error-prone non-homologous end joining or homology-directed repair. Zink Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), Clustered Regularly Interspaced Short Palindromic Repeats associated with Cas9 or Other CAS Endonucleases (CRISPR-Cas), homing endonucleases/meganucleases, megaTALs, base editors, and prime editors have all been developed and optimised for use in human cells with the goal of improving efficiency and translating to therapeutic.

ZFNs and TALENs are chimeric nucleases that produce DNA double-strand breaks that promote endogenous DNA repair systems. They are made up of programmable, sequence-specific DNA-binding modules coupled to a DNA cleavage domain. CRISPR-Cas, which is derived from antiviral defence mechanisms in archaea and bacteria, causes double strand DNA breaks at the spot targeted by a Single Guide RNA (sgRNA). CRISPR-Cas systems are evolving to include a wider range of Cas effectors. Meganucleases, which are homing endonucleases produced from I-CreI and I-CeuI, identify palindromic DNA sequences and cause DNA double-strand breaks, whereas megaTALs are designed chimeric proteins that combine homing endonucleases and TAL effector arrays. Base editing, which uses a catalytically dead Cas (dCas9) fused to an engineered reverse transcriptase and Prime Editing RNA (pegRNA) to target a site in the genome and provide a template for the desired edit, and prime editing, which uses dCas9 fused to an engineered reverse transcriptase and Prime Editing RNA (pegRNA) to target a site in the genome and provide a template for the desired edit.

CONCLUSION

The success of CAR T-cell immunotherapy in the treatment of B-cell malignancies has paved the way for a growing number of therapeutic options involving genetically altered immune cell therapies to treat cancer, infection, autoimmune, and other diseases.

Gene editing advances are combining with this result to vastly expand the options for enhancing immune cell potency by gene disruption or gene insertion.

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