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Review Article

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Gene-Editing Technologies in the Treatment of Inherited Metabolic Disorders

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Abstract
Inherited metabolic diseases (IMDs), or inborn errors of metabolism, are a varied set of genetic illnesses caused by pathogenic variations in enzymes, transporters, cofactors and other proteins involved in metabolic processes. Such problems may result in accumulation of toxic metabolites, shortage of critical metabolic products or disturbance of cellular homeostasis leading to progressive neurological, hepatic, cardiovascular and other systemic consequences. Although clinical outcomes have improved with dietary modification, pharmaceutical treatment, enzyme replacement therapy and organ transplantation, many IMDs remain difficult to cure and may require life-long management. Gene-editing technologies provide a promising method to tackle inherited illnesses by allowing the precise change of genomic sequences to fix pathogenic mutations, restore gene function, or decrease the generation of toxic metabolites. The major platforms include zinc-finger nucleases, transcription activator-like effector nucleases, CRISPR-associated nucleases, base editors and prime editors. Some metabolic illnesses affecting hepatic pathways, such as hereditary tyrosinaemia, ornithine transcarbamylase deficiency and phenylketonuria have shown treatment potential in preclinical investigations. However, clinical translation is limited by delivery efficiency, off-target modifications, unintentional genetic alterations, immunological responses and uncertainty surrounding long-term safety. This review is focused on the main genetic editing methods, its possible application in inherited metabolic diseases, existing limits and future perspectives for clinical application. Genetic editing may ultimately supplement or supplant traditional treatment but its suitability will have to be determined on a case-by-case basis for each condition and editing modality.

Keywords: *Base editing, CRISPR-Cas9, editing of genes, hereditary metabolic disorders, prime editing, genome therapy, metabolic diseases.*

Introduction

Inherited metabolic disorders (IMDs), also known as inborn errors of metabolism, are a broad range of genetic illnesses caused by deficiencies of enzymes, membrane transporters, cofactors, and other proteins required for normal biochemical function. These abnormalities are affecting metabolic processes involved in synthesis, breakdown, transport or recycling of biological substances. Their implications could be toxic accumulation of substrates, lack of necessary products, aberrant energy generation, and disturbance of cellular homeostasis. Clinical symptoms vary from neonatal metabolic crises to progressive neurologic deficits, liver dysfunction, cardiomyopathy, skeletal deformities and multiorgan illness [1,2].

For example, phenylketonuria, urea cycle abnormalities, glycogen storage diseases, organic acidemias, and lysosomal storage illnesses including Gaucher disease and Pompe disease. The severity of these disorders varies with the involved gene, the functional ramifications of the pathogenic variation, residual enzyme activity, and environmental or dietary variables [3].

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The goal of conventional management is to control metabolic abnormalities, prevent complications and improve quality of life. Therapeutic measures may comprise food restriction, supplementation with deficient products or cofactors, pharmaceutical treatment, enzyme replacement therapy, substrate reduction, or organ donation, depending on the condition. While these therapies have improved lifespan and illness control, they do not reliably repair the underlying genetic abnormality and may require lifelong administration, frequent monitoring or large financial resources. [4]

Gene-editing technologies have been proposed as viable treatments, because they may modify specific genomic sequences rather than merely compensating for the consequences of a genetic flaw. Editing might restore a functional gene, disrupt a damaging genetic sequence, insert a therapeutic sequence, or adjust gene regulation, depending on the platform and disease mechanism. Major techniques are zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), CRISPR-associated nucleases, base editing and prime editing [5].

The liver is a particularly attractive target for gene-editing research because it carries out a variety of metabolic tasks and produces circulating proteins and enzymes needed for systemic homeostasis. However, illnesses of the brain, skeletal muscle, kidney, bone marrow or other organ systems may necessitate alternate or adjunct delivery strategies [6]. This review focuses on major gene-editing tools and their mechanisms of action, applications in hereditary metabolic disorders, translational hurdles and possibilities for clinical use.

The Main Gene Edition Technologies

The clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) are one of the most thoroughly studied genome editing technologies. The method uses a guide RNA to guide the Cas9 nuclease to a complementary DNA sequence next to a suitable protospacer-adjacent motif. Cas9 cuts the DNA at a certain spot, creating a double-strand break.

The cell then repairs the break. The repair is mainly done via non-homologous end joining, or by homology directed repair if an appropriate repair template is available. Non-homologous end joining can create insertions or deletions that affect gene function, while homology-directed repair can allow for precise sequence correction or targeted insertion. The efficacy of these routes depend on the target tissue, cell type, delivery mechanism and experimental settings [3,4]. Inherited metabolic diseases can be treated with CRISPR-Cas9 by correcting disease-causing mutations, restoring production of functional proteins or disrupting genes that make toxic metabolites. The feasibility of targeted genome editing has been proven in preclinical research in animal models of hereditary tyrosinaemia type I, ornithine transcarbamylase deficiency and other metabolic disorders [7].

While CRISPR-Cas9 editing is a versatile tool, it can also introduce unintentional DNA modifications, such as off-target mutations and undesirable changes at the intended target site. Therefore, its therapeutic application needs to be carefully assessed for the accuracy of editing, genomic integrity, and long-term safety.

Zinc-finger nucleases are designed proteins made up of zinc-finger DNA-binding domains connected to a DNA-cleaving domain, often that of the FokI endonuclease. Correctly positioned nucleases bind to their target sequences and introduce a double strand DNA break.

This second break triggers cellular repair pathways, resulting in gene disruption or, under appropriate conditions, the precise correction of the sequence. ZFNs were among the first programmable nucleases produced for therapeutic genome editing and have helped to pave the way for targeted treatments for Monogenic Diseases [8].

They may be used in inherited metabolic diseases to fix faulty genes or interrupt specified sequences to modify production of metabolites. However, constructing an efficient pair of ZFNs can be technically challenging, with concerns like as specificity, editing efficiency, manufacturing complexity and delivery still relevant.

Transcription activator-like effector nucleases (TALENs) are composed of a DNA-binding domain derived from transcription activator-like effectors and a DNA cleavage domain. Targeted genomic alteration is possible because the binding domains can be tailored to identify chosen DNA sequences.

Similar to ZFNs, TALENs create double-strand breaks that are healed by the host cellular machinery. Thus, they may facilitate gene disruption, sequence correction or targeted insertion, provided that adequate repair conditions are maintained.
TALENs provide a valuable alternative to CRISPR-Cas9 because they recognise DNA differently than guide RNA-directed nucleases. However, the size of editing components and complexity of engineering and administering paired nucleases may limit their usage for specific therapeutic applications [9].

Meganucleases are special endonucleases which identify relatively long DNA sequences and cleave DNA at specified locations. The recognition properties of these can give significant targeted specificity and are hence of importance for genome engineering. However, engineering meganucleases to target new genomic sites can be technically difficult. They

therefore play a less important role in current therapeutic genome-editing research than CRISPR-based technologies. The use of these in hereditary metabolic diseases is dependent on the availability of appropriate target sequences, effective delivery and acceptable safety profiles [10].

Base editing allows the conversion of one DNA base pair into another at precise genomic locations without a traditional double-strand DNA break. Most current base editors are a fusion of a catalytically altered Cas protein and a nucleotide modifying enzyme. Cytosine base editors (CBEs) might mediate C→T conversions while adenine base editors (ABEs) could mediate A→G conversions at appropriate target sites [11].

This method is especially useful for inherited metabolic diseases due to single-nucleotide mutations. If a pathogenic variant can be repaired by an existing base-editing method, the technique might be able to restore protein function while bypassing some of the hazards related to double-strand DNA breaks.

Preclinical studies have investigated base editing for metabolic liver disease and phenylketonuria. But not all pathogenic variations can be addressed by current base editors. Possible drawbacks include off-target editing, unintended DNA or RNA alterations, limited editing windows, and dependence on appropriate target sequences [12].

Prime editing is a programmable genome-editing technique that combines a Cas9 nickase with a reverse transcriptase and a specific prime-editing guide RNA. The guide RNA directs the editing complex to the target sequence and acts as a template for the installation of the desired DNA modification.

Prime editing can introduce all 12 possible single-base substitutions and selected tiny insertions or deletions, depending on the system and target, without the need of a typical double-strand DNA break or a separate donor DNA template [13]. Its versatility makes prime editing suitable for inherited metabolic diseases with harmful mutations that are not easily addressable with standard base editors. However, editing efficiency is target and cell-type dependent, and distribution of the comparatively large editing machinery remains a major hurdle. Further preclinical and clinical studies are needed to assess its safety, durability and therapeutic efficacy in specific metabolic illnesses.

Epigenome editing is a targeted approach to modify gene activity without affecting the underlying DNA. It generally uses catalytically dead Cas proteins or other DNA targeting systems fused to regulatory domains that can activate or inhibit transcription or modify local chromatin states.

This method may be effective in cases where increased expression of a functioning gene, decreased production of a deleterious protein, or modification of a compensatory metabolic pathway might be beneficial for illness outcome. Epigenome editing may have a different risk–benefit ratio than permanent genomic editing because the DNA sequence itself is not necessarily altered [14]. But the persistence, specificity and reversibility of epigenetic modifications need to be carefully studied. Epigenome editing is still a young approach and should be separated from technologies that directly fix harmful DNA variations.

Therapeutic Use in Inherited Metabolic Disorders

Phenylketonuria is a hereditary metabolic condition caused most often by pathogenic mutations in the PAH gene, which encodes the enzyme phenylalanine hydroxylase. If this enzyme is not present, phenylalanine cannot be changed into tyrosine and high levels of phenylalanine can cause serious brain damage if not properly managed. Current management is mostly based on dietary phenylalanine limitation, specific nutritional products and chosen pharmacologic therapies in suitable individuals. These therapies can improve results significantly but may be difficult and burdensome to sustain metabolic control.

Genetic modification may repair harmful PAH variations or restore adequate hepatic phenylalanine hydroxylase activity to improve metabolic regulation. Proof of concept for this strategy has been demonstrated in preclinical studies using genome editing and precision editing technologies [5] However, therapeutic benefit must be established by sustained biochemical regulation, preservation of brain function and acceptable long-term safety.[15]

Hereditary tyrosinaemia type I is caused by a deficit of the enzyme fumarylacetoacetate hydrolase, which is encoded by the FAH gene. The illness leads to a buildup of toxic metabolites that can harm the liver and kidneys and increase the risk of severe consequences.

In experimental animals, gene modification has been explored as a technique of restoring functional FAH expression. In some preclinical situations, targeted correction of a pathogenic sequence may confer a selective advantage to corrected hepatocytes, allowing them to grow in the liver [16].

This observation underscores a crucial therapeutic principle, namely that the fraction of successfully edited cells necessary for clinical benefit can be dependent on the biological properties of the disease and whether corrected cells possess a survival/growth advantage. However, the effectiveness and safety of this approach in humans need to be further evaluated. Urea cycle disorders are caused by abnormalities in enzymes or transport proteins that transform nitrogenous waste into

urea for excretion. One of the best studied cases is ornithine transcarbamylase deficiency, because severe impairment can lead to hyperammonaemia, brain damage and life-threatening metabolic decompensation.

Genome-editing methods have been tested in experimental models to restore functioning enzyme expression or to modify critical liver pathways. These results highlight the potential of targeted editing to address the underlying genetic aetiology rather than only relying on ammonia-lowering medications and dietary management [17]. However, successful therapy would require enough correction in relevant cells, sufficient enzyme activity and rapid and sustained reduction of ammonia production. Any therapy would also have to reduce the potential of treatment-related liver harm or unintended genetic changes.

Lysosomal storage disorders are a set of diseases that arise from defects in enzymes or other proteins that are essential for lysosomal function. Examples include Gaucher disease and Pompe disease which can cause progressive hepatic, haematological, skeletal, muscular or neurological issues.

Gene-editing techniques may involve correcting the damaged gene in the affected cells or altering selected cells to make and release a functional enzyme. The proposed procedures are disorder-dependent and involve direct editing of liver cells, ex vivo alteration of haematopoietic stem cells or targeted modification of other important tissues.

The choice of method depends on the distribution of the enzyme, the organs involved, the likelihood of cross-correction by ingestion of released enzyme, and whether the condition affects the central nervous system. diverse lysosomal disorders have diverse biological properties and hence an approach that is beneficial for one illness cannot be immediately expected to be effective for another18].

Gene modification is also being researched for specific glycogen storage illnesses, organic acidemias, and disorders of aberrant lipid or amino acid metabolism. Possible uses include replacement of defective enzyme activity, reduction in formation of hazardous metabolites and alteration of pathways compensating for the main biochemical defect. The therapeutic effectiveness of these techniques will depend on the molecular cause of each disease, the ability to target the relevant tissue and the extent of functional repair required to improve clinical results. Most of these applications are still in the preclinical phase, rather than being established in clinical practice.

DELIVERY OF GENE EDITION

The effective delivery is necessary to translate the gene-editing technologies into therapies for hereditary metabolic diseases. The editing apparatus needs to be able to reach the target cells, enter them in a functioning condition and generate the desired genomic mutation without unacceptable toxicity.

Viral vectors including adeno-associated virus (AAV) vectors have been explored for delivery of gene-editing components to targeted tissues. Under the right settings AAV vectors can efficiently target the liver, making them intriguing for certain metabolic illnesses.

However, constraints include pre-existing immunity, immunological reactions after delivery, limited packaging capacity, and challenges in long-term expression of editing components. The continued expression of the nuclease may raise the chance of off-target editing. These considerations are important in selecting a viral distribution platform [19]. Lipid nanoparticles can be used to transfer nucleic acids (e.g., messenger RNA encoding an editing enzyme and guide RNA) to target cells. Transient delivery profile may reduce persistent exposure to editing components. Liver-directed lipid nanoparticle administration is particularly relevant in metabolic illnesses because hepatic correction may provide systemic benefit. However, transport efficiency can vary between tissues and cell types and repeated administration, immunological responses, biodistribution and manufacturing consistency need thorough evaluation [20]. Ex vivo editing entails taking a specific cell type from a patient, altering the cells in a laboratory environment, testing the modified cell population, and returning the cells to the patient when clinically suitable.

This approach could potentially be used to diseases involving haematopoietic stem cells or other cell types which can be harvested and reinfused. This allows examination of the efficiency of editing and of specified safety features before administration. However, the harvesting of cells, the processing, conditioning regimens, transplant-related problems, and the maintenance of long-term cell function may all contribute to a significant clinical and economic burden.

Possible Benefits and Advantages

Editing genes presents various possible improvements over current management of inherited metabolic diseases. Secondly, it might tackle the genetic issue directly, instead than dealing primarily with its metabolic effects. Second, effective editing may have persistent therapeutic impact, perhaps lowering the need for lifelong treatment. Third, several tactics may restore endogenous protein production in its native cellular milieu. Fourth, programmable editing systems can be customised for particular harmful variations and disease processes. Finally, the ability to make targeted changes in particular genes may allow therapeutic intervention in diseases where conventional medicines give only partial control.

But these possible benefits should not be taken as evidence that gene modification would definitely heal all hereditary metabolic diseases. The extent and durability of benefit will rely on disease cause, the effectively altered cells, the extent of residual or restored protein function and the safety of the delivery technique [21].

Problems and Limitations

A key risk is that an editing method could alter genomic locations that were not meant to be altered. These alterations can damage important genes, affect gene control or contribute to cellular malfunction. DNA repair in the intended target can result in unanticipated insertions, deletions or broader genomic changes even in the target.

Therefore, thorough evaluation of editing specificity and genomic integrity should be carried out before clinical application. Many hereditary metabolic diseases are polyorgan yet some need to be corrected solely in a particular tissue. But getting enough editing in the right cells is a huge task. For example, liver-directed editing may be appropriate for some hepatic metabolic abnormalities but may not be sufficient to address disorders that involve the brain, skeletal muscle or other tissues.

Patients can mount immunological responses to viral vectors, Cas proteins or other components of the editing mechanism. Delivery materials may also induce inflammatory responses or tissue harm. These hazards may limit the dose that can be given and complicate repeat therapy.

The effects of permanent genome alteration may be slow to become apparent. Long-term monitoring is essential to evaluate if therapeutic results are sustained and to assess if delayed adverse events including clonal expansion or tumour-related occurrences develop. The durability of treatment may also be limited if altered cells do not survive or the disease affects tissues that cannot be effectively regenerated.

Personalised genome-editing therapies demand huge investments in research, production, regulatory review and clinical monitoring. These expenses can act as a barrier to access, especially in low- and middle-income countries where the infrastructure for specialised genetic testing and treatment may be inadequate.

Ethical concerns are informed consent, fair access, handling of uncertain longterm dangers, and the difference between somatic editing and heritable germline alteration. Clinical development for hereditary metabolic disorders ought to focus on properly controlled somatic therapies, not presuming germline change is necessary or acceptable.

Conclusions

Gene-editing technologies are a viable avenue for the treatment of inherited metabolic disorders since they offer the potential to fix harmful variations, restore enzyme activity, or change disease-associated metabolic pathways. There are other methods of genomic or gene regulation modification such as CRISPR-Cas9, ZFNs, TALENs, base editing, prime editing, and epigenome editing each having its advantages and disadvantages. Preclinical data in some metabolic diseases support additional exploration, especially where it is possible to correct specifically in the liver or other accessible cell populations to achieve meaningful biochemical improvement. But gene modification is not yet a proven therapy for hereditary metabolic diseases in general. Major constraints include delivery restrictions, unexpected genetic alterations, immunological responses, expense, and lack of clarity concerning long-term effects. Rigorous clinical examination, ethical oversight, equitable access and ongoing research will be critical to determine the patients and conditions most likely to benefit. With these precautions in place, genetic editing could be a significant component of precision medicine for selected inherited metabolic illnesses.

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