

Review

CRISPR-Based Gene Therapy for Type 2 Diabetic Neuropathy

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Abstract: Type 2 diabetic neuropathy represents the most prevalent and debilitating chronic complication associated with diabetes mellitus. The condition is fundamentally characterized by a complex interplay of chronic hyperglycemia, lipid metabolism disorders, severe oxidative stress, systemic inflammation, mitochondrial dysfunction, Schwann cell degradation, neurovascular disease, and abnormal insulin signaling pathways. Traditional therapeutic interventions primarily focus on basic blood sugar control, analgesia, neurotrophic therapy, and improving circulation; however, these conventional approaches fail to significantly suppress the underlying neurological damage or reverse disease progression. Emerging as a revolutionary gene-editing tool, CRISPR technology offers unprecedented advantages, including robust targeting capabilities, high programmability, and flexible intervention strategies. These attributes provide highly promising research perspectives for the precise and curative treatment of type 2 diabetic neuropathy. This comprehensive review systematically examines the potential application value of CRISPR technology in managing oxidative stress, inhibiting inflammatory signaling cascades, repairing Schwann cell damage, restoring myelin sheaths, increasing neurotrophic support, correcting metabolic abnormalities, and remodeling neurovascular structures based on the primary pathogenesis of the disease. Furthermore, we critically discuss the current technological bottlenecks hindering clinical translation, specifically focusing on in vivo delivery challenges, in vitro editing and reinfusion limitations, and the complexities of combination therapies. Ultimately, while CRISPR stands as a top-performing technology for the gene therapy of diabetic neuropathies, further critical breakthroughs must be achieved in off-target effect mitigation, accurate delivery mechanisms, long-term safety, and multi-target synergistic control to successfully advance these applications from basic laboratory research to widespread clinical practice.

Keywords: CRISPR; type 2 diabetes; diabetic neuropathy; gene therapy; schwann cells

1. Introduction

Type 2 diabetes is one of the most prevalent chronic metabolic diseases encountered in clinical practice. Its incidence increases with advancing age, excessive caloric intake, and sedentary lifestyles, making it a significant public health concern. Long-term hypoglycemia not only disrupts glucose, lipid, and protein metabolism but also causes chronic damage to multiple organs and systems. Among the complications, diabetic neuropathy is one of the most common and complex, often manifesting as asymmetrical distal peripheral nerve damage. Patients frequently report symptoms such as numbness, tingling, burning sensations, reduced sensitivity, abnormal gait, and leg weakness [1]. In severe cases, complications can escalate to diabetic foot, chronic ulcers, infections, and even amputation, severely impacting patients' quality of life and increasing societal healthcare costs. Current clinical treatments primarily focus on glycemic control, neurotrophic therapy, improved microcirculation, and symptomatic pain relief. However, these approaches are largely palliative, aiming to alleviate symptoms and slow disease progression, without addressing the underlying neurological structural damage or functional impairment. This underscores the urgent need for innovative treatments that directly target the pathological mechanisms of the disease. Pathologically, type 2 diabetes is not a singular condition but rather a complex interplay of multiple mechanisms driven

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by prolonged metabolic imbalances. These include chronic hypoglycemia, abnormal lipid metabolism, oxidative stress, inflammatory responses, mitochondrial dysfunction, Schwann cell damage, neurovascular complications, and disrupted insulin signaling. The multifactorial and multistage nature of these pathological pathways highlights the limitations of traditional treatment models. Precision interventions targeting specific genes and molecular pathways offer a promising alternative. Recent advancements in gene editing technologies, such as CRISPR, have demonstrated high specificity, programmability, and efficiency. Beyond traditional gene knockout methods, these technologies now encompass base editing, prime editing, and transcriptional regulation, providing novel insights into the precision treatment of complex diseases. For type 2 diabetic neuropathy, CRISPR technology holds potential in modulating oxidative stress, suppressing inflammatory responses, promoting myelin repair, enhancing neurotrophic support, and optimizing the brain microenvironment. This study aims to systematically explore the mechanisms underlying type 2 diabetes, its pathogenesis, potential therapeutic targets, treatment pathways, and clinical interventions, offering a comprehensive perspective on advancing treatment strategies for this debilitating condition.

2. Pathogenesis of Type 2 Diabetic Neuropathy

2.1. Neurotoxicity Caused by Chronic Hyperglycemia and Glucose-Lipid Metabolism Disorders

The primary cause of type 2 diabetic neuropathy is prolonged exposure to elevated blood glucose levels. Chronic hyperglycemia activates the polyol metabolic pathway, converting glucose into sorbitol via aldose reductase. This process increases intracellular osmotic pressure and reduces inositol levels, which subsequently disrupts Na⁺/K⁺-ATPase activity and compromises the stability of nerve cell membranes. Additionally, elevated glucose levels lead to the formation of advanced glycation end products (AGEs), which exacerbate oxidative stress and trigger inflammatory responses through receptor-mediated mechanisms. Diabetes is also associated with lipid metabolism disorders, where excessive free fatty acids induce lipotoxicity, impair mitochondrial function, and disrupt the energy balance within nerve cells, ultimately contributing to axonal degeneration. The prolonged disruption of glucose and lipid metabolism not only causes severe damage to nerve tissues but also diminishes the local repair mechanisms, serving as a critical initiating factor for the progression of diabetic neuropathy. Figure 1 illustrates the pathophysiological mechanisms underlying the symptoms of type 2 diabetic neuropathy, providing a comprehensive visual representation of these complex processes.

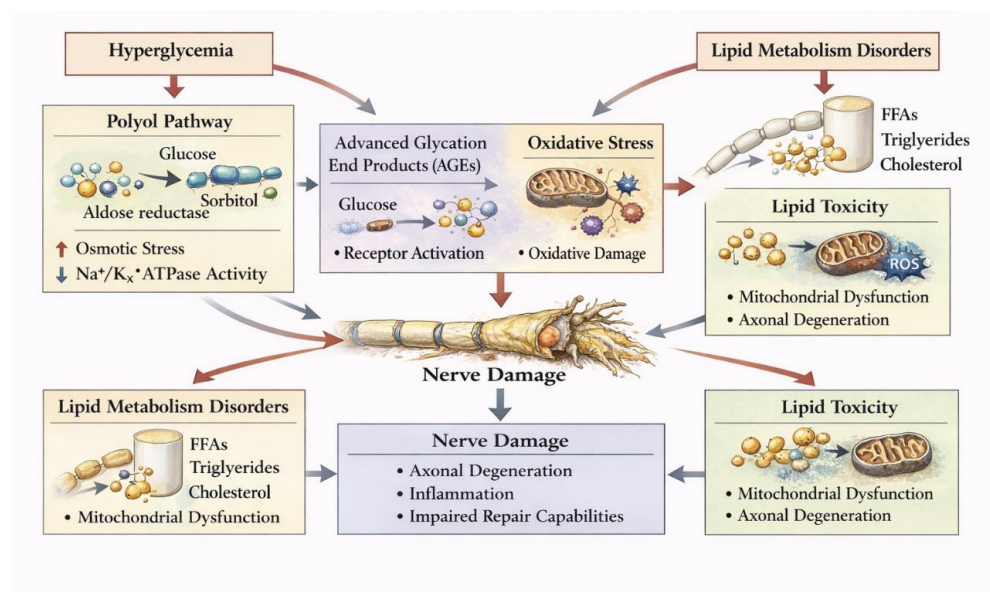


Figure 1. Pathophysiology of Type 2 Diabetic Neuropathy

2.2. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress plays a critical role in the development and progression of diabetes. Under conditions of elevated glucose levels, the mitochondrial electron transport chain becomes overwhelmed, leading to a significant reduction in reactive oxygen species (ROS) production. Simultaneously, intracellular antioxidant defense systems, including superoxide dismutase, catalase, and glutathione peroxidase, are compromised. This imbalance between oxidation and antioxidation contributes to cellular damage. Excessive ROS production can harm lipids, proteins, and DNA, resulting in structural and functional abnormalities within cells. Such damage degrades mitochondrial membrane potential and reduces ATP production, leaving nerve cells in a state of chronic energy deficiency. Neurons, due to their extended structure, rely heavily on mitochondria for energy. Persistent mitochondrial dysfunction can disrupt axonal transport, slow nerve conduction, and ultimately lead to neuronal apoptosis. Additionally, oxidative stress can exacerbate painful neuropathy by inhibiting pain-related ion channels and promoting synaptic sensitization, further complicating the condition.

2.3. Inflammatory Response and Imbalance of the Immune Microenvironment

Patients with Type 2 diabetes often experience chronic low-grade inflammation, which plays a significant role in the progression of diabetic neuropathy. Elevated glucose levels and advanced glycation end products (AGEs) activate signaling pathways such as NF- κ B, JAK/STAT, and NLRP3 inflammasomes, leading to the release of inflammatory molecules like TNF- α , IL-1 β , and IL-6. These inflammatory factors contribute to neuronal and Schwann cell damage and indirectly impair nerve function by disrupting endothelial cell activity and microcirculation. Furthermore, the interplay between inflammation and oxidative stress creates a self-perpetuating cycle that exacerbates diabetic neuropathies over time [2]. In cases of painful diabetic neuropathy, inflammatory mediators heighten the excitability of pain nerve fibers and amplify central sensitization, resulting in symptoms such as burning pain, tingling sensations, and hyperalgesia. This complex interaction underscores the importance of addressing both inflammation and oxidative stress in therapeutic strategies for managing diabetic neuropathies.

2.4. Schwann Cell Damage and Myelin Homeostasis Imbalance

Schwann cells are essential supportive components of peripheral nerves, playing pivotal roles in myelin formation, metabolic support, damage repair, and the secretion of neurotrophic factors. Under conditions of elevated glucose levels, these cells are prone to functional degradation due to oxidative stress, inflammatory responses, and metabolic reprogramming disorders. Such disruptions can manifest as inhibited proliferation, heightened apoptosis, abnormal differentiation, and reduced expression of myelin-associated proteins. Damage to Schwann cells compromises the structural integrity of the nerve fiber myelin sheath, weakening its electrical insulation properties and slowing nerve conduction velocity. Furthermore, their capacity to secrete critical neurotrophic hormones, such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF), becomes impaired, particularly during repair processes [1, 3]. This dysfunction is a significant pathological hallmark of diabetic neuropathy, highlighting Schwann cells as a promising target for future therapeutic interventions aimed at restoring nerve function and maintaining myelin homeostasis.

2.5. Neurovascular Lesions and Ischemia-Hypoxia Injury

Normal nerve function relies heavily on a consistent microcirculatory blood supply to maintain optimal performance. Insufficient blood concentrations can lead to damage in the microvessels of nerves, resulting in slow vasodilation, thickening of the basement membrane, reduced blood perfusion, and chronic ischemia-hypoxia in localized tissues. Prolonged under-perfusion of nerve tissue limits metabolic clearance, hampers nutrient delivery, and adversely affects axons and myelin sheaths. Furthermore, microvascular complications can hinder the efficiency of therapeutic drugs and the delivery of repair factors to the affected site [4, 5]. These disturbances in microcirculation not only contribute

to the onset of diseases but also play a significant role in the progression of chronic conditions, emphasizing the importance of maintaining vascular health in nerve function.

2.6. Abnormal Insulin Signaling and Insufficient Neurotrophic Support

Insulin plays a critical role not only in glucose metabolism but also in supporting brain development, axonal growth, synaptic plasticity, and the activity of neurotrophic factors [5]. In individuals with type 2 diabetes, insulin signaling becomes significantly impaired, leading to a reduction in protective pathways such as PI3K/Akt. This diminishes the resilience of nerve cells, making them more vulnerable to damage caused by elevated glucose levels, oxidative stress, and inflammation. Furthermore, insufficient insulin signaling adversely affects brain function, hindering nerve regeneration and overall neurological performance. Consequently, abnormal insulin signaling represents both a metabolic disorder and a pivotal factor in the progression of diabetic neuropathy, emphasizing the need for targeted therapeutic strategies to mitigate these effects.

3. Principles, Types, and Medical Applications of Crispr Technology

3.1. Basic Principles of the CRISPR/Cas System

CRISPR is a groundbreaking gene-editing technology originally derived from the immune defense mechanisms of prokaryotes, which protect against the invasion of foreign nucleic acids. This system employs guide RNA to direct the Cas protein, such as Cas9, to identify and cleave specific DNA sequences. The classic CRISPR/Cas9 system primarily consists of a single guide RNA and the Cas9 endonuclease. When the guide RNA matches the target gene sequence, Cas9 induces a double-strand break at the specified location in the DNA. Following this, the cell's natural repair mechanisms, either non-homologous end joining or homologous recombination, are activated to repair the break. This process enables researchers to precisely disrupt, insert, replace, or correct genes, facilitating targeted interventions for disease-related genetic abnormalities [6]. Such advancements hold immense potential for treating genetic disorders and advancing personalized medicine.

3.2. Main Types of Crispr Technology

CRISPR/Cas9 represents one of the most straightforward and recent advancements in gene-editing technology. It functions by inactivating target genes through the creation of insertion or deletion mutations, which occur via non-homologous end joining after inducing a double-strand break. This method is particularly effective for blocking pathogenic genes or disrupting abnormal pathways, making it widely applicable in research focused on disease mechanisms. Base editing, another innovative technique, enables precise modification of single bases using deaminases paired with inactivated Cas proteins [3]. This approach minimizes damage while achieving high accuracy, making it ideal for applications requiring fine-tuned genetic regulation. Lead editing technology, which utilizes leader editing enzymes and specific guide RNAs, allows for more complex genetic modifications, including sequence insertions, deletions, and substitutions. This method offers greater flexibility and precision, enabling the correction of specific mutations with enhanced accuracy compared to traditional Cas9 systems. CRISPRa and CRISPRi, in contrast, do not directly cut DNA but instead employ inactivated Cas proteins to modulate transcriptional activity. By upregulating protective genes or downregulating pro-pathological genes, these techniques hold significant promise for addressing complex chronic diseases, such as type 2 diabetic neuropathy, through targeted genetic interventions.

3.3. Advantages of Crispr Compared to Traditional Gene Therapy

Compared to traditional therapies that rely on introducing exogenous genes, CRISPR technology offers a more precise approach by targeting endogenous genes. This allows for tailored interventions such as gene knockout, activation, inhibition, or precise repair, depending on the specific requirements of a disease. Furthermore, advancements in high-quality Cas proteins and delivery systems continue to enhance the safety and expand the

potential applications of CRISPR. For complex, non-monogenous diseases like type 2 diabetic neuropathy, CRISPR not only functions as a tool to correct genetic errors but also as a mechanism to regulate abnormal pathological processes, offering a multifaceted approach to disease management.

3.4. The Basis of Crispr Applications in Metabolic and Neurological Diseases

CRISPR is extensively utilized in both mechanistic research and advanced therapeutic investigations targeting metabolic and neurological disorders. In the context of diabetes, CRISPR technology enables the screening of genes critical for pancreatic β -cell function, as well as the exploration of insulin resistance and glucose metabolism pathways. For neurological diseases, CRISPR offers potential treatments for a range of conditions, including neurodegenerative diseases, neuroinflammation, hereditary neuropathies, and neurodevelopmental abnormalities. These advancements have significantly contributed to the development of CRISPR-based applications for managing type 2 diabetic neuropathy, highlighting its transformative potential in addressing complex disease mechanisms and therapeutic challenges.

4. Potential Therapeutic Targets for Type 2 Diabetic Neuropathy Based on Crispr Technology

4.1. Editing Strategies Targeting Oxidative Stress Pathways

Oxidative stress pathways represent a promising avenue for therapeutic intervention in diabetic neuropathy. A critical regulator of cellular antioxidant activity is Nrf2, which governs the expression of several key antioxidant enzymes, including HO-1, NQO1, SOD, and GPX. Enhancing Nrf2 activity through CRISPR activation (CRISPRa) or suppressing the expression of pro-oxidative enzymes, such as members of the NOX family, via CRISPR interference (CRISPRi), could significantly reduce reactive oxygen species. This approach may improve mitochondrial function and protect against damage to neurons and Schwann cells, thereby mitigating the progression of diabetic neuropathy [7, 8].

4.2. Editing Strategies Targeting Inflammatory Pathways

Inflammation plays a critical role throughout the progression of diabetic neuropathy, with key inflammatory mediators such as NF- κ B, NLRP3, TNF- α , and IL-6 identified as potential therapeutic targets. Utilizing CRISPR technology to inhibit these major inflammatory pathways can significantly reduce chronic inflammation, thereby protecting nerve tissues from damage and alleviating the painful symptoms associated with neuropathy. Notably, targeting the NLRP3 inflammasome pathways has demonstrated efficacy in suppressing localized inflammation amplification and reducing pain sensitization, offering promising avenues for therapeutic intervention in managing diabetic neuropathy.

4.3. Editing Strategies Targeting Schwann Cell Protection and Myelin Repair

Schwann cell damage and myelin damage are among the most prevalent pathological changes observed in diabetic neuropathy. Key factors such as SOX10, EGR2, MPZ, and PMP22 play critical roles in Schwann cell differentiation and the process of myelination. Enhancing the expression of these factors or mitigating demyelination-related damage through advanced techniques like CRISPRa could significantly improve myelin homeostasis. This approach holds potential for promoting remyelination and restoring the functional integrity of affected neural pathways.

4.4. Editing Strategies Targeting Axonal Regeneration and Neurotrophic Factors

Neurotrophic factors are critical for promoting axonal regeneration and ensuring neuronal survival. In diabetic conditions, these factors, including NGF, BDNF, GDNF, and CNTF, are often underexpressed, leading to diminished repair mechanisms in damaged nerves. Enhancing the expression or activity of these neurotrophic factors, potentially through advanced techniques such as CRISPRa targeting their receptors, could significantly improve neuronal survival and axonal regeneration. This approach may

facilitate the recovery of sensory and motor functions, offering a promising avenue for addressing nerve damage in diabetic states.

4.5. *Upstream Editing Strategies Targeting Insulin Signaling and Metabolic Abnormalities*

Type 2 diabetic neuropathy is intricately linked to systemic metabolic conditions, which makes targeting upstream metabolic pathways a promising therapeutic strategy [9]. By editing pathways such as IRS1, PI3K/Akt, AMPK, PPAR γ , and SIRT1, it is possible to exert a multifaceted impact on the disease. These interventions can improve the local metabolic environment surrounding the nerves, while simultaneously promoting anti-inflammatory responses, reducing apoptosis, and maintaining mitochondrial homeostasis. Such approaches hold the potential to address the underlying causes of the condition, offering a more comprehensive and effective treatment paradigm.

4.6. *Editing Strategies Targeting Neurovascular Remodeling*

Neural microcirculatory diseases are increasingly recognized as pivotal factors in the progression of diabetes. Key molecules such as VEGF, eNOS, and HIF-1 α play essential roles in angiogenesis, regulation of blood flow, and adaptation to local hypoxia. Enhancing the microvascular remodeling capacity of nerves through advanced gene editing techniques holds significant potential for improving local blood and oxygen supply. This approach could also facilitate the clearance of metabolic waste, optimize nutrient transport, and create more favorable conditions for nerve repair and regeneration, thereby addressing critical aspects of diabetic complications.

5. **CRISPR-Based Therapeutic Pathway Design**

5.1. *Direct Editing of Neural Tissue Cells Strategy*

Direct *in vivo* editing involves the delivery of the CRISPR system directly to target cells within diseased tissues, such as neurons, Schwann cells, and endothelial cells [10]. This approach is advantageous due to its ability to act directly on the affected area, its relatively straightforward treatment process, and its potential for developing localized targeted therapies. However, significant challenges remain, including the low efficiency of current delivery systems, inadequate targeting precision, and the risk of off-target effects. Addressing these issues is critical for advancing the therapeutic potential of this strategy and ensuring its safe application in clinical settings.

5.2. *Indirect Therapy Strategy Using Stem Cells or Engineered Cells*

Another potential approach involves modifying stem cells or engineered supporting cells using CRISPR technology *in vitro*, followed by their transplantation into the affected region. This strategy can utilize mesenchymal stem cells, induced pluripotent stem cell-derived supporting cells, or Schwann-like stem cells to achieve enhanced anti-inflammatory, antioxidant, and regenerative effects. Rigorous *in vitro* screening and quality control processes are essential to ensure the safety, efficacy, and patient-specific uniqueness of these cells. Such measures can significantly improve therapeutic outcomes while minimizing potential risks associated with cell-based interventions.

5.3. *Comparison of *in Vivo* Delivery and *in Vitro* Editing and Reinfusion Modes*

In vivo delivery offers a simpler approach and is theoretically more suitable for rapid local intervention, as it allows for direct targeting and potentially safer application [7]. On the other hand, *in vitro* editing followed by reinfusion involves a more complex process but provides the advantage of precise screening, verification, and reinfusion of modified cells. Each method has distinct advantages and limitations, and the optimal choice may vary depending on factors such as the stage of the disease, the extent of tissue damage, and the specific therapeutic target being addressed.

5.4. *Combined Treatment Mode*

Type 2 diabetic neuropathy is characterized by the involvement of multiple pathological mechanisms, making it challenging to address with a single therapeutic approach. While gene editing technologies like CRISPR offer precise interventions, their

efficacy is significantly enhanced when combined with other treatments. These include glucose regulation therapies, neurotrophic factors, anti-inflammatory agents, tissue engineering scaffolds, and rehabilitation strategies. This integrated approach, termed "precise editing + full treatment," aims to restore both the structural integrity and functional capacity of neural tissues, offering a more comprehensive solution to this complex condition.

6. Current Bottlenecks and Development Prospects of CRISPR-Based Treatment for Type 2 Diabetic Neuropathy

One of the most significant challenges associated with CRISPR technology is the issue of off-target effects. When the guide RNA pairs incorrectly with a non-target sequence, unintended gene editing can occur, potentially leading to unpredictable and harmful long-term side effects. This concern is particularly critical for neurological diseases, as neural tissue lacks the ability to regenerate, necessitating extensive safety and stability monitoring over time following treatment. Current delivery systems, including adeno-associated viruses, lipid nanoparticles, polymers, and exosomes, face limitations in their ability to efficiently target peripheral nerves, penetrate tissues, and maintain long-term expression control. Furthermore, type 2 diabetes patients often experience microcirculatory complications, which can hinder the delivery systems from effectively reaching the lesion site. Consequently, achieving precise and efficient delivery remains a significant obstacle to the clinical translation of CRISPR-based therapies for diabetic neuropathy.

Type 2 diabetes is a multifactorial disease, not attributable to a single gene or pathway defect [11]. Instead, it involves a complex interplay of numerous factors, stages, and cell types. While single-target gene editing may address specific mechanisms, it is insufficient to reverse the overall pathology of the disease. A more comprehensive approach would involve multi-target, staged interventions that address key regulatory networks. Gene editing for chronic, non-fatal diseases like type 2 diabetes requires careful consideration of the balance between potential benefits and risks. This includes ensuring patient informed consent, establishing robust long-term follow-up systems, developing efficacy evaluation metrics, and adhering to stringent regulatory review processes. These measures are essential prerequisites for the clinical application of CRISPR technology in treating such conditions.

In the future, advancements in multi-cell sequencing, multiomics, and artificial intelligence algorithms may enable the identification of critical regulatory points at various stages of diabetic neuropathy. Co-editing these targets through multi-target approaches could significantly enhance treatment outcomes by addressing pathways such as oxidative stress, inflammatory responses, neurotrophic factor regulation, and metabolic disorders [12]. These strategies would better align with the complex nature of chronic diseases like type 2 diabetes. Additionally, the development of high-fidelity Cas proteins, base editing, prime editing, and virus-free delivery technologies holds promise for improving the safety and precision of CRISPR-based therapies. As these technologies mature, they may pave the way for more personalized treatment models tailored to individual patients. Such models could consider factors like metabolic profiles, stages of neurological damage, and clinical phenotypic variations, ultimately advancing gene therapy for type 2 diabetic neuropathy toward the realm of precision medicine.

7. Conclusion

Type 2 diabetic neuropathy represents a severe and persistent chronic condition marked by a complex interplay of pathological mechanisms, including elevated glucose toxicity, oxidative stress, inflammatory responses, Schwann cell damage, microvascular complications, and disruptions in insulin signaling associated with prolonged metabolic disorders. Current therapeutic approaches, while capable of mitigating symptoms and decelerating disease progression, remain inadequate in addressing the repair of structural

neurological damage. CRISPR technology, a highly precise, adaptable, and programmable genetic and molecular network-based tool, has emerged as a promising avenue for targeting the underlying pathological processes of diabetic neuropathies at the genetic and molecular levels. Its potential applications are extensive, encompassing antioxidant defense, reduction of inflammation, repair of myelin sheaths, enhancement of neurotrophic support, regulation of metabolic pathways, and improvement of microcirculation. These advancements offer significant theoretical and developmental prospects for the field. However, the implementation of CRISPR-based therapies faces substantial challenges, including off-target genetic modifications, inefficient delivery mechanisms, difficulties in tracking neural tissues, the heterogeneous nature of the disease, and ethical considerations. To advance this technology toward clinical application, future research must prioritize the development of multi-target synergistic regulatory strategies, the creation of safer and more efficient gene-editing platforms, the design of precise delivery systems, and the establishment of personalized treatment models. These efforts are essential for facilitating the transition of CRISPR-based gene therapies for type 2 diabetic neuropathy from experimental exploration to practical clinical use, ultimately improving patient outcomes and quality of life.

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