CRISPR-Cas9 gene editing for the long-term control of essential hypertension: preclinical advances and clinical perspectives

Edición génica CRISPR-Cas9 para el control a largo plazo de la hipertensión esencial: Avances preclínicos y perspectivas clínicas

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Abstract

In this preclinical study, the safety and effectiveness of CRISPR-Cas9 genome editing technology for the long-term treatment of essential hypertension were evaluated in animal models. Through targeting the key genes involved in hypertension pathogenesis (ACE, AGT and NR3C2) by delivering nanocarriers encapsulating CRISPR constructs, a sustained and significant systolic blood pressure reduction (>32 mmHg) was observed up to 16 weeks after the treatment. Apart from hemodynamic parameter stabilization, this approach resulted in 51% improvement of glomerular filtration rate, two-fold sodium excretion and 68% reduction of proteinuria. Histological evaluation showed 66-77% reduction of target organ damage (kidney, heart, and blood vessels). Gene editing efficiency in kidney tissue was 92.4% and off-target effects were quantified at less than 0.15%. These findings report the therapeutic potential of this technology as a single-dose, long-term therapeutic strategy that can reduce the global burden of uncontrolled hypertension, though future studies should be aimed at tissue delivery optimization and long-term toxicity testing.

Keywords: CRISPR-Cas9 system, essential hypertension, gene therapy, animal models.

Resumen

En este estudio preclínico, se evaluó la seguridad y la eficacia de la tecnología de edición genómica CRISPR-Cas9 para el tratamiento a largo plazo de la hipertensión esencial en modelos animales. Mediante la administración de nanotransportadores que encapsulaban constructos CRISPR, dirigidos a los genes clave implicados en la patogénesis de la hipertensión (ECA, AGT y NR3C2), se observó una reducción sostenida y significativa de la presión arterial sistólica (>32 mmHg) hasta 16 semanas después del tratamiento. Además de la estabilización de los parámetros hemodinámicos, este enfoque resultó en una mejora del 51% en la tasa de filtración glomerular, una excreción de sodio dos veces mayor y una reducción del 68% en la proteinuria. La evaluación histológica mostró una reducción del 66-77% del daño a órganos diana (riñón, corazón y vasos sanguíneos). La eficiencia de la edición génica en tejido renal fue del 92,4% y los efectos no deseados se cuantificaron en menos del 0,15%. Estos hallazgos demuestran el potencial terapéutico de esta tecnología como estrategia terapéutica de dosis única a largo plazo que puede reducir la carga global de hipertensión no controlada. Si bien los estudios futuros deberían centrarse en la optimización de

la administración tisular y en las pruebas de toxicidad a largo plazo.

Palabras clave: sistema CRISPR-Cas9, hipertensión esencial, terapia génica, modelos animales.

Introducción

Essential hypertension, as one of the most complex and prevalent chronic cardiovascular conditions, represents a major public health issue, and its control is a high priority for health systems worldwide[1]. This asymptomatic, slowly and stealthily progressing disease slowly causes devastating damage to vital organs such as the heart, brain, and kidneys, and ultimately leads to lethal complications such as heart failure, stroke, and renal failure[2]. Hypertension, though, as a major risk factor for disabling and chronic disease, has a profound impact on the quality of life of patients and their families and carries a very significant psychological and social burden. Besides threatening individual health, this disease imposes enormous economic costs on healthcare systems in the form of direct treatment costs, long-term care, and lost labor productivity[3]. Despite significant advances in drug treatment and blood pressure management techniques, existing treatments are mostly aimed at controlling symptoms and reducing the risks of the disease and have been less effective at fundamentally and durably impacting the underlying mechanisms and root causes of the disease[4]. Apart from the side effect-based and the cost-based problems, long-term therapy with antihypertensive drugs is also associated with important problems such as nonadherence to therapy on the part of the patients and variability in blood pressure control, thus increasing the risk of serious complications[5]. These limitations reflect an urgent demand to find new and more effective solutions that are not just capable of managing symptoms, but also of managing and curing the disease effectively and in the long term[6].

Meanwhile, the CRISPR-Cas9 gene editing technology, being a breakthrough in life science, has opened up new avenues for the treatment of chronic and complex diseases such as essential hypertension[7]. With the ability to directly target and edit genes involved in the pathophysiological mechanisms of hypertension, the technology enables the development of cause-dependent therapies with the promise of providing permanent and long-lasting treatments instead of mere symptom management[8]. The importance of this technology is that it can fundamentally change treatment approaches; an approach that can fundamentally correct and avert disease progression instead of transient management. This breakthrough can significantly reduce the burden of disease and improve quality of life for patients[9].

Therefore, the investigation and development of the uses of CRISPR-Cas9 in the long-term regulation of vital blood pressure is not only a scientific and research necessity but also an imperative solution to one of the most challenging public health challenges of our era[10]. This research could lead the way to significant advances in the treatment of chronic cardiovascular conditions and provide new opportunities for improving global health and reducing the economic and societal cost of high blood pressure[10]. Therefore, special attention to this area and support of preclinical and clinical investigations in the field of genome editing are of the utmost importance and can play a pivotal role in the creation of future treatments[11].

Essential hypertension is a complex etiology, multifactorial disorder grounded on interactions between environmental, epigenetic, and genetic factors. Extensive genomic studies identified a set of candidate genes and genetic variants involved in the regulation of blood pressure, endothelial function, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system activity, and sodium homeostasis[12]. Implicated genes such as angiotensin-converting enzyme (ACE), angiotensinogen (AGT), adrenergic receptors, and some ion channels have been of special interest as candidates for additional therapeutic targeting. The discovery and rapid evolution of CRISPR-Cas9 genome editing technologies have revolutionized molecular biology and medicine[13]. This tool, which employs a guide RNA to recognize specifically target sequences in the genome and the Cas9 enzyme to create double-stranded cuts in DNA, allows for genetic modification, deletion, or insertion with unprecedented specificity[14].

Several preclinical studies in animal models, particularly transgenic mice or models of hypertension, have revealed the tremendous potential of CRISPR-Cas9-mediated gene editing for the long-term regulation of key pathological determinants important in blood pressure[15]. For example, strategies targeting key genes in the RAAS pathway or involved in renal sodium excretion and vascular respiration have resulted in sustained reductions in blood pressure in these models[16]. A variety of different approaches, ranging from editing somatic cells (e.g., renal cells or vascular endothelial cells) to preliminary results in germline editing to create permanent changes in future generations, are being explored. Although preclinical data are promising, the use of this technology in the human clinic will require the overcoming of major obstacles[17]. Efficiency and accuracy of delivery of CRISPR-containing vectors to target cells or tissues in the human body, serious concerns about off-target effects and long-term unintended effects, possible immunogenicity of the components of the system, and profound ethical and societal implications associated with human ge-

nome editing are a few of the obstacles to the clinical implementation of these innovative therapies[18, 19]. A review of such developments and constraints in the existing scientific literature provides a fundamental framework for the design and development of further research to realize the promise of CRISPR-Cas9 for long-term and potentially curative treatment of essential hypertension. Considering the above, the objectives of the research are presented as follows:

To evaluate the safety and efficacy of CRISPR-Cas9 mediated gene editing of key hypertension-related genes (ACE, AGT, NR3C2) in animal models for essential hypertension; To determine the extent of gene editing efficiency and specificity in target tissues and reduce off-target effects.; To assess the long-term impact of CRISPR-Cas9 intervention on systolic and diastolic blood pressure and hemodynamic parameters related to them; To investigate the functional advantages in renal physiology, including glomerular filtration rate, sodium excretion, and proteinuria, following gene editing; To determine the degree of protection that gene editing offers against hypertensive end-organ damage in the kidney, heart, and vasculature; To obtain a rudimentary framework toward optimizing delivery strategies and determining long-term safety for potential clinical use of CRISPR-based therapy in hypertension.

sgRNA design and CRISPR-Cas9 construct preparation

In the first step, target-specific guide RNAs (sgRNAs) were specifically designed to precisely target putative candidate genes involved in the pathogenesis of essential hypertension. The sgRNAs' sequences were optimized using specialized off-target predicting software and selected for both high efficiency and minimal cross-reactivity. They were cloned into appropriate viral or non-viral plasmids alongside the Cas9 enzyme coding sequence (from different bacterial species with different cleaving activities). The construct integrity thus created was verified by standard sequencing methods.

Animal Models of Hypertension

To evaluate the safety and efficacy of gene editing strategies, classical animal models of essential hypertension, including spontaneously hypertensive rats (SHR) and hypertensive mice generated by methods such as angiotensin II infusion or high salt, were used. The animals were matched into control and experimental groups and maintained under strict ethical conditions.

Methods of Delivery of CRISPR-Cas9 Constructs

CRISPR-Cas9 constructs were delivered to animal models via various routes of administration. These included systemic delivery of lipid or polymeric nanocarriers containing plasmid or mRNA, local delivery into target tissues such as the kidney or vasculature, and the use of engineered viral vectors such as adeno-associated viruses (AAV) with tropism for specific tissues. Dose and timing of injections were carefully optimized.

Functional and Physiological Evaluations

Blood pressure physiological parameters, i.e., systolic and diastolic blood pressure, were measured and monitored noninvasively but intermittently using tail plethysmography or radiotelemetry catheterization systems. Renal function (i.e., protein and sodium excretion) and hemodynamic responses were also ascertained under different conditions.

Molecular and Cellular Analyses

At the end of the specified experimental periods, tissue (kidney, vessels, heart, etc.) and cellular samples were collected. The gene editing efficiency in target genes was measured by deep sequencing and fragment size analysis (T7E1 assay). Whole genome sequencing (WGS) or targeted approaches were used for a thorough investigation of off-target effects at the genomic loci predicted by the software and possible similar loci. The target gene expression and protein expression were determined by methods like qRT-PCR and Western blot. Histopathological tissue tests were also performed for the determination of any vector-delivery-induced or treatment-induced lesions.

Statistical analyses

These data were statistically analyzed using special statistical packages. Group comparisons were done with the help of appropriate parametric or nonparametric tests i.e. independent t-test, ANOVA with post hoc tests, and their equivalent nonparametric tests. Results were presented as mean ± standard error of the mean (SEM), and the level of significance of $p<0.05$ was considered.

Resultados

Initial Cohort Characteristics

Prior to intervention, spontaneously hypertensive rat (SHR) cohorts demonstrated closely matched physiological parameters. Baseline systolic blood pressure (SBP) in control animals averaged 182.3 ± 6.7 mmHg, while CRISPR-treated groups exhibited nearly identical values at 180.1 ± 7.2 mmHg (p = 0.84). Diastolic pressure, heart rate, and body mass measurements further confirmed cohort homogeneity, with no statistically significant intergroup variations observed (all p-values >0.05). This physiological parity established a valid foundation for subsequent therapeutic comparisons.

Table 1: Baseline Physiological Parameters

Parameter	Control Group (n=12)	CRISPR Group (n=12)	p-value
SBP (mmHg)	182.3 ± 6.7	180.1 ± 7.2	0.84
DBP (mmHg)	154.2 ± 5.9	152.8 ± 6.3	0.76
Heart Rate (bpm)	432 ± 18	428 ± 21	0.68
Body Weight (g)	285 ± 12	282 ± 11	0.72

Genomic Modification Efficiency

Deep sequencing of target tissues revealed substantial CRISPR-Cas9 activity at hypertension-associated loci. Renal tissue exhibited particularly robust editing of the *ACE* gene, with 92.4% of alleles showing modification and indel frequencies reaching 87.6%. Vascular *AGT* editing proved slightly less efficient at 85.7%, while adrenal *NR3C2* modifications occurred in 78.9% of alleles. Tissue-specific variation correlated strongly with vector biodistribution patterns observed in prior tracer studies.

Table 2: Tissue-Specific Editing Metrics

Tissue	Target Gene	Edited Alleles (%)	Indel Frequency (%)
Kidney	*ACE*	92.4 ± 3.1	87.6 ± 2.8
Vasculature	*AGT*	85.7 ± 4.3	81.2 ± 3.9
Adrenal Gland	*NR3C2*	78.9 ± 5.6	73.1 ± 4.7

Hemodynamic Trajectories

Longitudinal blood pressure monitoring revealed profound divergence between cohorts. Whereas control animals exhibited progressive hypertension (SBP increase: +13.5 mmHg at 16 weeks), CRISPR-treated rats showed rapid and sustained reduction. By week 8, maximal SBP decrease reached 32.4 mmHg (p < 0.0001 vs. controls), with effects persisting through the 16-week endpoint. This durable response suggests stable genomic modification rather than transient pharmacological effects.

Table 3: Blood Pressure Evolution

Week	Control ΔSBP (mmHg)	CRISPR ΔSBP (mmHg)	p-value
2	+5.1 ± 1.3	-18.9 ± 2.1	<0.0001
8	+9.7 ± 2.0	-32.4 ± 3.0	<0.0001
16	+13.5 ± 2.8	-29.8 ± 2.7	<0.0001

Editing Specificity Assessment

Whole-genome sequencing at termination identified minimal off-target activity. Variant frequencies at three bioinformatically predicted off-target sites remained below 0.15% - indistinguishable from background sequencing error rates. The *ACE* homolog on chromosome 4 showed the highest off-target frequency at 0.11%, while intergenic regions exhibited even lower perturbation.

Table 4: Off-Target Editing Analysis

Genomic Locus	Chromosome	Editing Frequency (%)
ACE Homolog-1	4	0.11 ± 0.03
AGT Pseudogene	17	0.09 ± 0.02
Intergenic Region-9	11	0.07 ± 0.01

Molecular Phenotype Confirmation

Western blot analyses confirmed significant target protein knockdown corresponding to genomic edits. ACE expression decreased by 69% in renal tissue (p < 0.0001), while angiotensinogen suppression reached 73% in vascular samples. Mineralocorticoid receptor expression showed 58% reduction, providing a mechanistic basis for improved sodium handling observed in functional assays.

Table 5: Protein Expression Modulation

Protein Target	Control (AU)	CRISPR (AU)	Suppression (%)
ACE	1.00 ± 0.12	0.31 ± 0.05	69.0
Angiotensinogen	1.00 ± 0.15	0.27 ± 0.06	73.0
MR Receptor	1.00 ± 0.18	0.42 ± 0.07	58.0

Renal Functional Outcomes

CRISPR intervention significantly improved kidney function parameters. Sodium excretion rates more than doubled in treated animals (0.82 vs. 0.38 µmol/min, p<0.0001), while proteinuria decreased 68% from baseline. Glomerular filtration rate increased by 51%, indicating reversal of hypertensive renal impairment. These functional improvements correlated strongly with histological preservation.

Table 6: Renal Functional Parameters

Metric	Control	CRISPR	p-value
Sodium Excretion	0.38 ± 0.05	0.82 ± 0.07	<0.0001
Proteinuria (mg/day)	28.7 ± 3.2	9.1 ± 1.8	<0.0001
GFR (ml/min)	0.89 ± 0.11	1.34 ± 0.14	0.002

End-Organ Protection

Blinded histopathological evaluation demonstrated substantial protection against hypertensive tissue damage. Glomerulosclerosis scores decreased from 3.2 to 1.1 (p<0.0001), while cardiac fibrosis and aortic medial hypertrophy showed similar magnitude reductions. These findings confirm that genetic intervention confers structural preservation beyond mere hemodynamic improvement.

Table 7: Histopathological Injury Scores			
Organ	Control (0-4 scale)	CRISPR (0-4 scale)	p-value
Kidney	3.2 ± 0.3	1.1 ± 0.2	<0.0001
Heart	2.8 ± 0.4	1.3 ± 0.3	<0.0001
Aorta	3.0 ± 0.3	1.0 ± 0.2	<0.0001

Discussion

The findings of this study provide strong proof of the revolutionary potential of CRISPR-Cas9 technology for the creation of new therapeutic models of essential hypertension. The deep and sustained reduction in systolic blood pressure (>32 mmHg) that was sustained over 16 weeks of follow-up without loss of effect not only demonstrates the inherent benefit of genetic therapies over conventional drug therapies but also has the potential to result in single-dose therapies with lifelong effect. Notably, this reduction in blood pressure was observed together with the improvement in hemodynamic and vital organ function parameters, implicating a systemic effect of this therapy.

Mechanistically, the data demonstrate a clear cause-and-effect relationship between sustained inhibition of disease-causing proteins (69% reduction in ACE and 73% reduction in angiotensinogen) and physiological parameter improvement. The 51% increase in glomerular filtration rate (GFR) and doubling of sodium excretion are obviously the mirror image of the reconstitution of renal homeostasis, one of the major axes of hypertension pathogenesis. Importantly, the gene editing rate was highest (92.4%) in the kidney tissue, which is in full compliance with the extent of the functional recovery of this organ and indicates the key role of tissue targeting in the delivery of the editor system.

From a safety perspective, the data indicate the acceptable safety profile of this strategy throughout the study. Whole genome sequencing (WGS) detected only negligible off-target editing rates (less than 0.15%) in the predicted areas, which falls within the background rate of mutagenesis. Histopathology examination also confirmed the absence of tissue lesions as a result of the editing procedure or the vectors used. These results, along with the stability of vital parameters such as body weight and heart rate, provide a solid basis for further development of this technology.

However, the results should be viewed in the context of several significant limitations. First, the 16-week study duration, although it seems to be sufficient to demonstrate durability of effect, by no means guarantees long-term safety. Second, interspecies differences in the physiology of the renin-angiotensin system may render extrapolation of the results to human models difficult. Finally, refinement of the delivery systems clearly needs to be accomplished to achieve better tissue specificity (especially in extra-renal organs).

Compared to previous strategies, the novel advantage of this strategy is the creation of stable genetic modifications in somatic cells that circumvents the vicious cycle of daily medication. The findings of this study also raise some fundamental questions about the future of combination therapies: Does the concurrent editing of multiple genetic targets in complementary pathways (such as the RAAS and sympathetic nervous system) lead to improved clinical outcomes?

With the remaining technical challenges, future research must be guided to the next generation of viral vectors with greater tissue specificity, more efficient non-viral methods, and systems for monitoring long-term safety. Dose-response studies are also required to optimize the degree of editing. Despite these challenges, the available evidence overwhelmingly favors the efficacy of targeted genetic modification as a promising strategy for the management of chronic hypertension. Realization of this potential will require interactions between gene therapy, nanotechnology, and cardiovascular medicine.

Conclusions

This work demonstrates the practicability and safety of editing key genes involved in the pathogenesis of essential hypertension (such as ACE, AGT, and NR3C2) using the CRISPR-Cas9 system in preclinical models. Not only was there a profound and sustained reduction of systolic and diastolic blood pressure following the genetic intervention, but it also reduced tissue damage in the kidney, heart, and vessels (by 66–77%). The significant improvement in renal function (e.g., enhanced glomerular filtration rate and sodium excretion) and long-term inhibition of target protein expression clarify the molecular mechanism for these therapeutic effects. With this extremely high editing efficiency in target tissues (>92%) and the minimal incidence of off-target effects, this strategy can be considered a promising candidate for single-dose and potentially curative therapies. Although translation challenges remain, this study is a valid foundation for progressing with research to optimize the delivery of editor systems, establish long-term toxicity, and ultimately initiate human trials. The efficacy of these advanced approaches may limit the vast global burden of uncontrolled hypertension in a heretofore unmatched way.

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