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LETTER TO THE EDITOR Open Access

Letter: The risk-benefit balance of CRISPR-Cas screening systems in gene editing and targeted cancer therapy

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Dear Editor,

I read with great interest the research conducted by Mingming Qin and colleagues, which highlights the advantages and potential barriers of the CRISPR system in precision medicine [1]. While the study outlines the benefits of CRISPR for gene editing and cancer therapy, it falls short of exploring the complexities these issues present in clinical practice and their implications for therapeutic efficacy and patient safety. The challenges identified—such as low delivery efficiency of lentiviral and AAV vectors, off-target effects, unintended mutations, and limitations in target specificity—threaten not only the effectiveness of gene editing but also the risk of triggering unintended systemic responses, including immune activation, inflammation, and dysregulation of apoptosis. These factors are closely tied to the treatment's success and safety profile.This paper aims to analyze the clinical ramifications of these technical bottlenecks and propose potential optimization strategies to advance gene editing applications in cancer treatment.

See the article "CRISPR-Cas and CRISPR-based screening system for precise gene editing and targeted cancer therapy" in volume 22, 516.

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Gene therapy shows immense potential in inducing apoptosis in cancer cells; however, its clinical application faces numerous challenges regarding safety and efficacy related to systemic adverse reactions. Gene editing technologies can precisely target cancer cells, yet potential side effects—such as myocardial infarction, stroke, and systemic inflammation—pose significant health risks (as shown in Fig. 1). These complications stem from the inherent complexity of gene regulation, underscoring the need for careful evaluation and mitigation of unintended consequences.

Haapaniemi et al. [2] discovered that utilizing CRISPR-Cas9 genome editing in human retinal pigment epithelial cells induced a p53-mediated DNA damage response and cell cycle arrest, resulting in the selective elimination of cells with a functional p53 pathway. This finding suggests that numerous critical cancer-related genes may exhibit diverse biological functions across different tissues. Such multifunctionality implies that targeting these genes could inadvertently impact other vital organ systems. For instance, the tumor suppressor gene p53 plays a crucial role in inhibiting tumorigenesis by promoting apoptosis, while also regulating stress responses in healthy tissues. However, excessive activation of p53 may lead to apoptosis in non-cancerous cells, particularly in essential organs like the heart and brain, potentially resulting in severe cardiovascular or neurological complications.

While CRISPR-Cas9 offers unprecedented precision, off-target effects remain an undeniable risk. These unintended genetic modifications can lead to dysfunctional proteins and provoke excessive immune responses or widespread inflammation. Such hyperactive immune reactions often coincide with systemic inflammation,

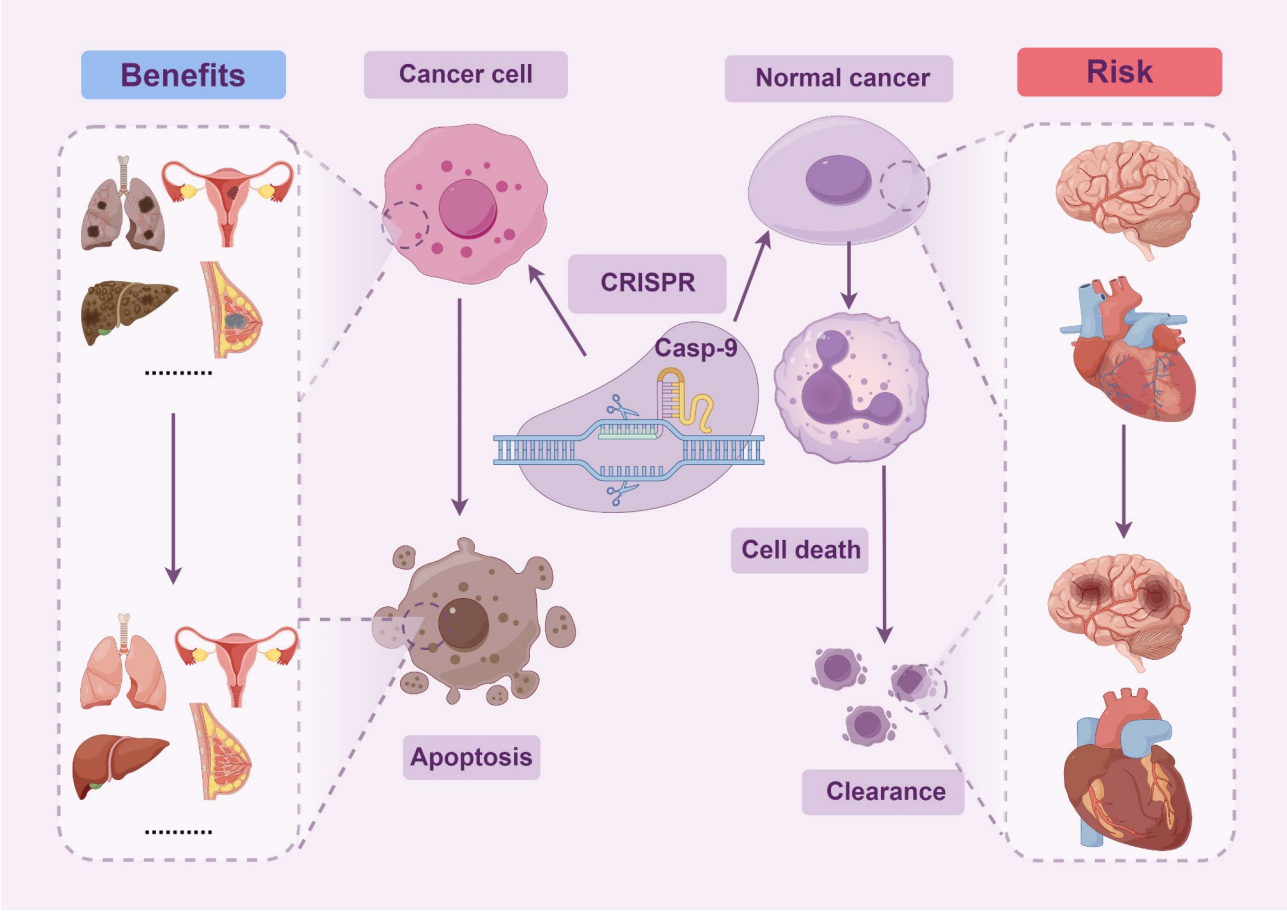

Fig. 1 The CRISPR-Cas screening system in gene editing and its benefits and risks in targeted cancer therapy. The left side illustrates the benefits of this gene therapy in treating malignant tumors, while the right side highlights the potential side effects on the heart and brain, including conditions such as myocardial infarction and stroke (by Figdraw2.0)

which can further damage essential organs and increase the risk of myocardial infarction or stroke.

Another central challenge is the nonspecific amplification of apoptotic signals. Pathways employed to induce apoptosis in cancer cells, such as the BAX/BCL2 axis or caspase cascades, also play significant roles in regulating apoptosis in healthy cells. Overactivation of these pathways can adversely affect healthy cells, particularly in sensitive organs, leading to irreversible damage. For gene therapy, this collateral damage heightens the risk of cardiovascular and neurological complications [3].

Lek et al. [4] treated a patient with Duchenne muscular dystrophy (DMD) using recombinant adeno-associated virus, which subsequently resulted in mild cardiac dysfunction, pericardial effusion, acute respiratory distress syndrome (ARDS), and ultimately, cardiac arrest leading to the patient's death. While Viral vector delivery systems are widely used in gene therapy; however, they may provoke excessive activation of the immune system, leading to systemic inflammatory responses [5]. Lentiviral or AAV vectors can sometimes trigger acute or chronic immune reactions, exacerbating tissue damage. For organs like the heart and brain, any form of immune overreaction can have catastrophic consequences, including myocardial infarction, stroke, or even death. Furthermore, the interplay between apoptotic pathways and immune regulatory networks, such as the NF-κB signaling pathway, may initiate excessive inflammatory responses and thrombotic events, significantly jeopardizing patient safety.

To balance efficacy and risk in cancer gene therapy, there is an urgent need for more precise strategies. Developing next-generation gene editing tools that reduce off-target effects and enhance target specificity is crucial. Employing tissue-specific delivery systems can help concentrate treatment on cancer cells while minimizing impacts on healthy tissues. Utilizing tumor-specific promoters can facilitate selective gene expression in cancer cells, thereby reducing potential threats to normal cells. Additionally, using anti-inflammatory drugs or cytoprotective agents may alleviate complications arising from excessive immune activation. Introducing personalized

treatment strategies based on patients' unique genetic profiles can further optimize therapeutic outcomes and reduce adverse reactions.

In conclusion, while gene therapy holds groundbreaking potential for inducing apoptosis in cancer cells, its clinical application must maintain a cautious balance between therapeutic benefits and potential risks. By enhancing gene editing precision, optimizing tissue-specific delivery, and incorporating personalized treatment approaches, future gene therapies can maximize efficacy while significantly mitigating the risks of severe adverse reactions. This will ultimately advance the safe and effective application of gene therapy in cancer treatment.

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Author disclosure
The author is currently the Chief Physician of the First Affiliated Hospital of Gannan Medical University and a visiting scholar at Weill Cornell Medical College, USA.

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