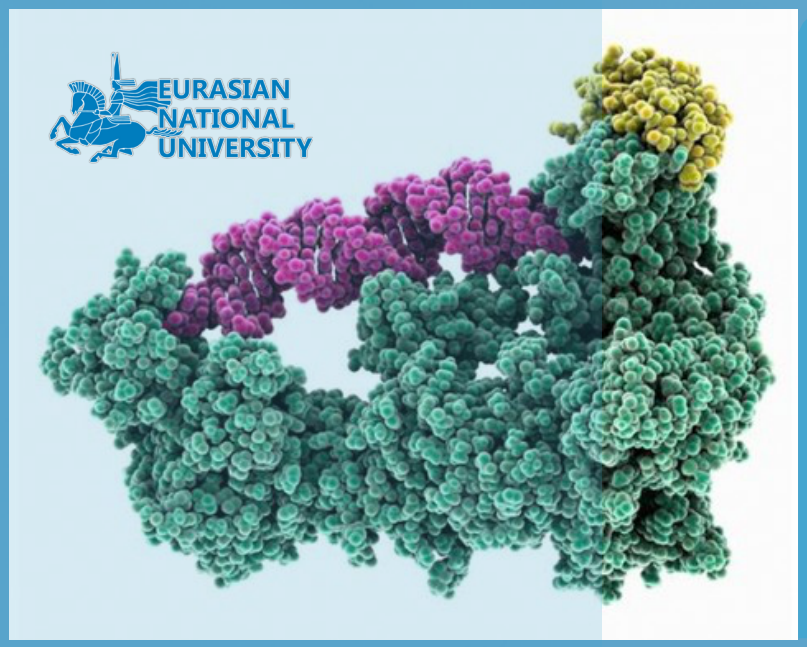
ҒЫЛЫМ ЖӘНЕ ЖОҒАРЫ БІЛІМ МИНИСТРЛІГІ
МИНИСТЕРСТВО НАУКИ И ВЫСШЕГО ОБРАЗОВАНИЯ



Л.Н. ГУМИЛЕВ АТЫНДАҒЫ
ЕУРАЗИЯ ҰЛТТЫҚ УНИВЕРСИТЕТІ

ЕВРАЗИЙСКИЙ НАЦИОНАЛЬНЫЙ
УНИВЕРСИТЕТ ИМЕНИ
Л.Н. ГУМИЛЕВА

"ОМАРОВ ОҚУЛАРЫ: XXI ҒАСЫРДЫҢ БИОЛОГИЯ ЖӘНЕ БИОТЕХНОЛОГИЯСЫ" АТТЫ ХАЛЫҚАРАЛЫҚ ҒЫЛЫМИ ФОРУМНЫҢ БАЯНДАМАЛАР ЖИНАҒЫ

СБОРНИК МАТЕРИАЛОВ МЕЖДУНАРОДНОГО НАУЧНОГО ФОРУМА "ОМАРОВСКИЕ ЧТЕНИЯ: БИОЛОГИЯ И БИОТЕХНОЛОГИЯ XXI ВЕКА"

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Жинақ «Омаров оқулары: XXI ғасыр биология және биотехнологиясы» атты халықаралық ғылыми форумына қатысушылардың баяндамаларымен құрастырылған. Бұл басылымда биология, биотехнология, молекулалық биология және генетиканың маңызды мәселелері қарастырылған. Жинақ ғылыми қызметкерлерге, PhD докторанттарға, магистранттарға, сәйкес мамандықтағы студенттерге арналған.

Сборник составлен по материалам, представленным участниками международного научного форума «Омаровские чтения: Биология и биотехнология XXI века». Издание освещает актуальные вопросы биологии, биотехнологии, молекулярной биологии и генетики. Сборник рассчитан на научных работников, PhD докторантов, магистрантов, студентов соответствующих специальностей.

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Берілген сурет бойынша, жоғары температуралық стресс вирустық инфеекцияның төмендеуіне, яғни TBSV репликациясын тежейтіні туралы тұжырым жасауға болады. Бұл жоғары температураның өсімдіктің қорғаныс механизмдерін белсендіріп, сондай-ақ морфологиялық, физиологиялық, молекулярлық жауапты туратынын айтады.

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Пайдаланылған әдебиеттер тізімі:

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Using CRISPR cas-9 to treat cancer: A Review

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Abstract

CRISPR-Cas9 technology has rapidly emerged as a versatile tool in genetic engineering, offering precise gene editing capabilities with unprecedented accuracy and efficiency. Originally discovered as a microbial defense mechanism(1), CRISPR-Cas9 has been ingeniously repurposed by scientists to target and modify specific genes within the human genome. This groundbreaking technology holds immense promise in significantly impacting cancer treatment by enabling the selective editing of genes associated with tumorigenesis and drug resistance,

potentially leading to more effective therapeutic interventions. In this article, we provide a comprehensive review of the current landscape of CRISPR-Cas9 applications in cancer research and treatment, highlighting its transformative potential in combating this formidable disease (2)

Introduction

Cancer is a devastating disease that claims the lives of millions of people each year. According to the World Health Organization cancer is the second leading cause of mortality in the world responsible for an estimated ten million deaths in 2020(3). At the same time, the treatment is also improving by using various genetic engineering methods such as modifying T-killer cells to enhance their ability to fight against cancer better. Traditional cancer treatments, like surgery to remove tumors, often lack specificity and come with side effects. Consequently, contemporary oncology is prioritizing the development of therapies that are more targeted and safer. (4,5) This shift has led to the emergence of other techniques. Furthermore, the advent of precise gene editing tools represents a milestone, opening doors to treatment modalities that can directly target the genes driving the uncontrolled growth and survival of cancer cells. But curing cancer is challenging due to the complex mechanisms and because of the diversity of cancer types and their ability to adapt to any environment it is hard to detect mutated genes and finding a universal cure is still impossible.(6) But CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), first discovered in E. coli in 1987, fundamentally changed our understanding of DNA and cancer therapy. Unlike other genetic engineering techniques, the use of CRISPR-Cas9 has improved throughout the years. With its unparalleled precision, CRISPR-Cas9 holds the potential to revolutionize cancer therapy by enabling targeted gene editing to eradicate cancerous cells while sparing healthy tissue(7). Because of the specificity and efficacy CRISPR-Cas9 become a significant advancement in biochemistry. In this article, we will review CRISPR-Cas9 and its applications in cancer therapy and research also basic mechanisms of this technique

Mechanisms of CRISPR

For centuries we did not know about how short repeat sequences work. But in 2005 scientists found out that these sequences are part of an immune system in bacteria(8). Thus, they concluded that this CRISPR/Cas9 technology originated from a fascinating immune defense mechanism observed in bacteria and archaea, providing them with protection against invading nucleic acids like viruses and phages. This system, known as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) along with the Cas9 enzyme, has gained significant attention in genetic engineering. Typically, CRISPR/Cas systems are classified into three main types, each comprising various subgroups. Among these, the type II CRISPR/Cas system is most employed for gene editing. It consists of three key components: Cas9, CRISPR RNA (crRNA), and transactivating crRNA (tracrRNA). The crRNA and tracrRNA molecules join to form a duplex structure called guide RNA (gRNA)(9). To streamline the process of genome engineering, this gRNA can be replaced by a synthetic fused chimeric single gRNA (sgRNA), making CRISPR/Cas9 technology more user-friendly and accessible. In the realm of genetic engineering, the single guide RNA (sgRNA) plays a pivotal role(10). Crafted with precision, it boasts a distinctive twenty base-pair (bp) sequence meticulously tailored to complement the target DNA site. For compatibility with the Cas9 protein, the sequence must be followed by a concise DNA segment called “protospacer-adjacent motif” (PAM) which is a short DNA sequence, usually 2 to 6 nucleotides, located near the target DNA sequence that Cas9 needs to cut**.** Upon expression within the cell, the sgRNA joins forces with the Cas9 nuclease, forming a formidable ribonucleoprotein (RNP) complex(11). Guided by the sgRNA, this dynamic duo navigates to the designated target DNA site with remarkable accuracy. The incision, occurring within the protospacer, occurs with surgical precision, precisely three nucleotides upstream of the PAM, yielding blunt ends. Facilitated by the RuvC and HNH active-site motifs of Cas9, this cleavage simultaneously targets both the (−) and (+) DNA strands. Subsequently, the cell's repair machinery springs into action, using one of two primary mechanisms—homology-directed repair (HDR) or non-homologous end joining (NHEJ). Homology-directed repair (HDR): This process

uses a donor DNA template to accurately repair the DNA double-strand break (DSB)(12). It is used for precise genome editing, such as introducing specific sequences or mutations. Non-homologous end joining (NHEJ): This mechanism is more common but less precise. It tends to insert or delete nucleotides at the DSB site, often causing frameshift mutations. It is useful for inducing gene knockouts. Also, this kind of mutation can be dangerous because of the randomness of the repair mechanism(12,13).

Overall, CRISPR/Cas9 holds a big promise in the field of genetic engineering. It is much easier to use, and design compared to older methods (ZFNs and TALENs)(14). Traditional methods rely on engineering proteins for each target gene. But CRISPR/Cas9 uses sgRNA instead. The RNA acts like a search term, providing Cas protein with the right spot in the DNA.Cas9 then makes a clean-cut at that location. Allowing scientists to introduce precise changes.

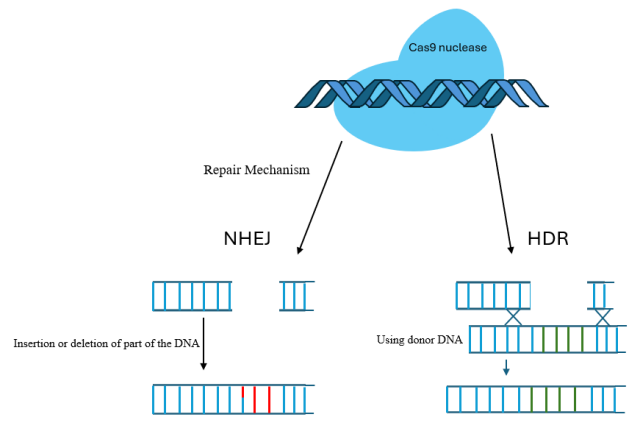

Fig 1. Two possible pathways for repairing a double-strand break in DNA: non-homologous end joining (NHEJ) and homology-directed repair (HDR).

CRISPR/Cas9 in cancer therapy

Finding a cure for cancer is still a complex problem. Despite improvements, there are still obstacles to overcome before CRISPR-Cas9 can be widely adopted in cancer therapy. One major challenge is delivering the CRISPR-Cas9 system accurately and efficiently into the target cells. In the context of cancer therapy, CRISPR-Cas9 offers diverse benefits. One important use is its potential to disable or change oncogenes, which are genes that promote cancer growth(15). By targeting and modifying these genes, CRISPR-Cas9 has the potential to slow down or even halt tumor growth. Earlier gene editing tools like TALENs and ZFNs were used for cancer treatment, but they may not have been as specific in targeting the exact epigenetic modifications associated with the disease(16). However, there has been a significant advancement in the field of immunology. Scientists introduced genetically engineered T-killer cells which are called CAR-T cells. Using the strength of the patient's own immune system, CAR T-cell therapy is a ground-breaking method of treating cancer. The creation of chimeric antigen receptors (CARs) is crucial to this therapy(17). Chimeric antigen receptors (CARs) are the workhorses of CAR T-cell therapy. They are engineered proteins that combine functionalities from various parts of the immune system to give T cells the ability to recognize and target specific cancer cells(18). CAR-T cell therapy has shown great promise in treating blood cancers due to the ability of cancer cells to move freely throughout the bloodstream(5). However, solid tumors pose a challenge to therapy as the dense tumor microenvironment can prevent CAR-T cells from reaching all cancer cells(19) (20) Developing effective CAR-T cells targeting all cancer cells is a complex task due to the wide range of surface proteins in solid tumors(21). CAR T-cell therapies can sometimes lead to a condition called T-cell exhaustion, where the modified T cells gradually lose their

effectiveness over time(22). Additionally, these engineered T cells may not remain in the body for an extended period, which can limit their long-term impact on cancer treatment. But, with the help of CRISPR/Cas9, we can modify these CAR-T cells to be more persistent and potent(23). We can use CRISPR-Cas9 to eliminate genes that make CAR T cells less effective, such as genes that cause T-cell exhaustion, or insert genes that make CAR T cells more effective, such as genes that help them to survive and multiply. CRISPR can target genes like PD-1 or CTLA-4, which function as brakes on the immune system, allowing CAR T cells to function for longer periods (24).

Scientists can use CRISPR to modify an animal's genome, including inserting, deleting, or changing specific genes. GEMMs (Genetically Engineered Mouse Models) are a valuable tool in cancer research because they allow scientists to study the development and progression of cancer in a living organism. By creating mice with mutations that are known to cause cancer in humans, researchers can gain insights into the biology of cancer and test potential new therapies(25).

Conclusion

CRISPR-Cas9 technology has emerged as a revolutionary tool with immense potential for cancer treatment. Its exceptional precision allows for targeted editing of genes associated with tumorigenesis and drug resistance, paving the way for more effective therapeutic interventions. While challenges remain in delivery methods and ensuring long-term efficacy, the ongoing advancements in CRISPR-Cas9, particularly its use in engineering CAR-T cells, offer a ray of hope for a future with more successful and personalized cancer therapies. However, it is crucial to acknowledge the ethical considerations surrounding this powerful technology as we move forward in its development and application.

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БАТЫС ҚАЗАҚСТАН ОБЛЫСЫНДА КЕЗДЕСЕТІН ИКСОД КЕНЕЛЕРІНІҢ (*IXODIDAE, PARASITIFORMES*) ҚОРЕКТЕНУ ЕРЕКШЕЛІКТЕРІ

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Иксодид кенелері ұзақ уақыт қоректенетін уақытша эктопаразиттердің экологиялық тобына жатады [1], сондықтан өмірлік цикл иксодид төрт кезеңнен тұрады: жұмыртқа, личинка, нимфа және имаго. Личинкалар мен нимфаларда қанмен қанықканнан кейін балқу пайда болады, ал ересек аналықтар қанның көп мөлшерін ішеді, олардың массасы бірнеше есе артады.

Жердегі артроподтардың паразиттену түрлерін зерттеу барысында В. Н. Беклемишев (1970) түрдің тіршілік схемасы туралы тұжырымдама жасады [2].

Соңғысы түрдің өмірлік циклін, иесінің денесімен де, қоршаған ортамен де қарым-қатынастағы барлық кезеңдерінің ерекшеліктерін қамтиды.

Кейіннен Ю. С. Балашов бұл жіктеуді паразиттік-ие қатынастар негізінде кеңейтті [3].