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THE PROSPECTS AND CHALLENGES OF CRISPR/CAS9 GENE EDITING IN CANCER THERAPY: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Cancer remains one of the leading causes of death in Kazakhstan, and CRISPR/Cas9 offers possible solutions to treat it. Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) is a system bacteria use to cleave foreign in-vaders. This system has been considered promising for cancer therapeutics by allowing researchers to edit cancer cell genes.*

The system requires more trials, so it is essential to raise awareness of this technique for stu-dents and potential investors and highlight the current challenges that could be research opportuni-ties for researchers.

The study aimed to *analyze and provide up-to-date information from reputable scientific journals on the current use of the CRISPR/Cas9 system in cancer therapeutics for medical students and researchers. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics.*

Methods: *The scientific literature and databases (PubMed and the Nature Journal) were searched and analyzed using the CRISPR/Cas9 system in cancer therapy.*

Results: *The results of this research indicate that scientists should focus on improving the types and structure of the Cas protein as well as the delivery methods, including the non-viral deliv-ery methods (liposome-based particles, hybrid vectors, gold nanoparticles, and extracellular vesicles) to contribute to improving the current status of cancer therapeutics.*

Conclusion: *CRISPR/Cas9 is an important technique that is still fraught with challenges and should be turned into research opportunities. The current challenges include the form and structure of the Cas nuclease, the types of engineering (in vivo vs. ex vivo), and the varieties of delivery methods. Each delivery method type has pros and cons and requires further research. In particular, future studies should focus on non-viral vectors, such as liposome-based particles, extracellular vesi-cles, hybrid vesicles, and gold nanoparticles.*

Keywords: *CRISPR, Cas9, cancer, oncology, delivery vectors, nanoparticles.*

Introduction: Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) is a system used by bacteria to cleave foreign invaders. The system has been considered promising for cancer therapeutics by allowing researchers to edit cancer cell genes. The CRISPR/Cas9 gene editing system is essential in current cancer research and therapy because it offers possible cancer treatment solutions and is simple and easy to design [1].

One of the goals of this research paper was to analyze and provide the current information from reputable scientific journals about the current status of the use of the CRISPR/Cas9 system in cancer therapeutics for medical students, researchers, and everyone interested in the current progress in the field of genetic engineering and cancer treatment. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics. The results of this literature review should offer an overview of the current challenges that scientists could utilize for their future research, meaning that this literature review aims to provide a concise review of the current challenges, prospective solutions, their advantages, and disadvantages, which researchers could use to inform their future studies.

The CRISPR/Cas9 gene editing system is a cost-effective and efficient tool. Although there are areas for improvement, these challenges offer new avenues for studies for researchers who seek to discover novel cancer therapy techniques, thereby making a significant contribution to the field of genetic engineering and molecular biology. This literature review highlights the most significant aspects that need further research and enhancement to improve CRISPR/Cas9 system-based cancer therapy. The results of this future research will significantly contribute to cancer therapeutics. They may save lives, so addressing the challenges of implementing the CRISPR/Cas9 system for cancer treatment is essential.

The study aimed to analyze and provide information from reputable scientific journals about the current status of using the CRISPR/Cas9 system in cancer therapeutics for medical students and researchers. This research paper also highlights the challenges associated with implementing CRISPR/Cas9 in clinical settings for cancer therapeutics.

Materials and Methods: The scientific literature and databases, including PubMed and the famous and reputable Nature Journal, were searched and analyzed using the CRISPR/Cas9 system in cancer therapy. The articles' references were also examined for relevance and analyzed for additional material. The criteria for choosing the scientific articles included relevance to the given research questions and topic as well as the time of publication. Based on

the gathered literature, the articles were selected based on their exigence, relevance to the topic under study, and novelty. Finally, the articles were examined and utilized to find new information to answer the research questions posed in this article, namely, "To what extent and how successfully can the CRISPR-Cas9 gene editing system be applied in cancer therapeutics? What challenges do scientists face in the clinical application of CRISPR/Cas9 gene editing technology in cancer therapeutics that could be transformed into research opportunities?"

Results:

The CRISPR/Cas9 gene editing in cancer therapy. The CRISPR/Cas9 gene editing system has been utilized to enhance T-cell therapy using two types of DNA repair: nonhomologous end-joining repair and homologous recombination repair. The former has been employed to remove molecules, such as PD-1, which inhibit the function of T cells in targeting cancer cells [1]. Furthermore, editing based on homologous recombination repair of DNA has been used to insert a specialized CAR gene (chimeric antigen receptor) into the TCR alpha chain of T cells, thereby increasing their efficiency [1]. This modified version of T cells is reportedly more efficient than the T-cells produced in the usual way [2]. Both types of engineering require more trials and appear effective in therapy.

Furthermore, CRISPR/Cas9 has been used to improve the side effects of chimeric antigen receptor (CAR) T cells for treating solid cancer. Previously, chimeric antigen receptor T cells have been successfully utilized for blood cancer treatment [3]. These T cells are genetically modified to recognize the antigens on target cancer cells. Apart from being used in blood cancer research, they have also been the subject of research as a possible treatment for solid cancers. However, the treatment of solid cancer cells with T cells has proved more difficult compared with the treatment of blood cancer. The significant challenges have been the heterogeneous nature or the absence of a sufficient number of antigens on the solid cancer cells, most of which are located within the cells, making it hard for the T cells to recognize them [3]. These challenges have been addressed using the CRISPR/Cas9 gene editing tool.

CRISPR/Cas9 has efficiently alleviated some aspects of utilizing genetically engineered T cells in solid cancer therapeutics by neutralizing the negative consequences of cytokine release and rejecting graft T cells. Specifically, the system has been used to silence HLA-I and TCR of graft T cells to minimize the organism's rejection of such cells [3]. It means that it has allowed the possibility of utilizing graft T cells in cancer treatment without causing distress to the organism. In addition, CRISPR/Cas9 has also been used to modify cytokine cells and prevent autoimmune reactions, which could hurdle cancer therapeutics [3]. Nevertheless, some aspects of the therapeutics still need further research.

Apart from T cell therapy, the development of CRISPR/Cas9 has prompted new genetic engineering approaches, including the regulation of transcription, editing of single bases, and cleavage of messenger RNA [4]. For example, DCas9, a modified version of Cas9, shows the potential to regulate transcription [5]. This modified version differs from the regular one in being more specific and having less off-target effects. It regulates transcription by loading activating, repressing domains or epigenetic modification enzymes [6]. However, the process is complicated and may result in errors, leading to multiple proteins possibly being affected by the intervention. In this regard, the specificity of the tool and the off-target effects require further research.

The challenges with the implementation of CRISPR/Cas9 in clinical settings. The two types of engineering include in vivo and ex vivo, and in vivo, genetic engineering should be prioritized over ex vivo engineering. One of the reasons for this is that ex vivo genetic engineering of T cells poses several challenges for researchers. First, genetically modified T cells are costly [1]. In addition, the process involves complex procedures, making it challenging to implement in practice [1]. While it could be wise to continue researching both types of engineering, researchers should also focus on improving the methods of in vivo genetic engineering. For example, experiments involving mice have shown promise in modifying T cells in vivo using polymeric Nano carriers loaded with CAR genes [7]. Such experiments must be replicated since the in vivo delivery method appears more advantageous in enhancing delivery efficiency.

Researchers should also focus on enhancing the CRISPR/Cas9 system, including the forms it delivers. One challenge concerns the CRISPR/Cas9 system's bacterial nature and the presence of immunity against it in some people [8, 9]. Some people have previously been infected with the Cas protein derived from the bacteria. As a result, these people have immunity against the nuclease derived from these bacteria. It would eliminate the protease from their organisms and the inability to introduce any changes to the organism's genome [1]. Future studies could focus on alternative ways to deliver the system, including its delivery in mRNA. However, such delivery methods have yet to be researched and carried out on a wide scale and remain a possible avenue for future research [1].

There is a need to research the delivery methods (and vectors) of genetically engineered T cells into cancer cells. Nanoparticles based on lipids or polymers, adeno- and lentiviruses have been utilized to deliver CRISPR-edited T cells into solid tumors; however, none of the delivery methods have proven to target the tumor cells specifically [10, 11]. In addition, although the methods may deliver the cells into some parts of the tumor, it is difficult to ensure a sufficient concentration of the cells in the target tissues [3]. The delivery methods are said to be one of the most significant challenges with applying T cells engineered by CRISPR/Cas9 in solid cancer therapeutics.

Viruses are one of the delivery vectors, and viral delivery methods suffer from packaging problems. Scientists note that new viral vectors with a low ability to produce an immune response or non-viral vectors with higher specificity are needed [1]. The viral method of delivery may be unsafe for the host organism. Apart from safety issues, the difficulty lies in packing the nuclease into the virus [12]. Although shorter variants of the nuclease introduced into several viral particles have been studied, researchers could focus on further enhancing the safety and packaging of the material into viral particles in future studies [12].

Furthermore, non-viral delivery methods are more advantageous in several ways than viral methods. Firstly, the viral vectors suffer from packaging problems in that only short nucleases can be packaged into the viruses. By contrast, the non-viral CRISPR delivery vectors do not have packaging issues because the CRISPR/Cas9 systems can be delivered in various forms in non-viral vectors (these include mRNA, ribonucleoprotein (RNP), and plasmid DNA) [1]. In other words, non-viral vectors are not limited in the number of particles that can be packaged into them. Secondly, viruses are known to cause immune reactions in the host organism. By contrast, the non-viral vectors are supposed to cause less severe reactions from the host. Researchers claim that non-viral vectors are easy to design [1, 12]. Non-viral vector materials could include micelles, liposomes, and other nanoparticles [12]. Several studies have described the delivery targeting the molecules that can enter the cell membrane, including the cell-penetrating peptide and delivery to the cell's nucleus [12]. Nevertheless, scientists acknowledge that few or an insufficient number of trials have been conducted using non-viral vectors for CRISPR delivery.

Non-viral and hybrid vectors for the delivery of CRISPR/Cas9. One of the encouraging methods of delivery is liposome-based nanoparticles. Liposome-based nanoparticles comprise cholesterol, phospholipids, and other components [13]. The method is particularly suitable for the delivery of drugs to the liver because it is the leading site of lipid processing; however, the disadvantage of this method is that the drugs accumulate in the liver and may not reach other organs in the required amounts. In addition, there have been concerns about the immunogenicity of such vectors. Although some of these vectors could be prone to causing an immune reaction, scientists have utilized peptides and introduced modifications into non-viral vectors to avoid immune responses. As a result of the addition of proteins on the surface of the non-viral vectors, the vectors could withstand or avoid the immune system reaction of the host organism.

In addition, biofilms and extracellular vesicles, such as exosomes, have been introduced into non-viral vectors to avoid immune response. Extracellular vesicles, including micro vesicles and exosomes, participate in cell signaling, transporting the signaling molecules or genetic material from inside the cell to other cells [14]. Exosomes are membrane-bound vesicles arising from multivesicular bodies in organelles [15]. These vesicles transport biomolecules inside the cell and can transport almost any substance within the cell. Such vesicles can deliver the CRISPR/Cas9 system with high specificity. The method seems effective since the vesicles retain the host organism's proteins on their surfaces, minimizing the risk of developing immune reactions [16]. Because the surface of such vesicles closely resembles that of the host cells, these cells will likely be recognized by the host as its cells, thereby reducing the likelihood of rejection by the host organism. In addition, the specificity of such vesicles can be improved by adding particular molecules on their surfaces (aptamers or antibodies) [14]. For example, extracellular vesicles covered with Chimeric antigen receptors (CARs) have been used to target B cell cancer [17].

Furthermore, hybrids of different vectors could be utilized to minimize each vector's side effects and enhance them. For example, exosomes hybridized with AAV (adeno-associated virus) or liposomes could be used. The presence of the exosome should protect the vector from being recognized by the host's immune system [18]. Such hybrid vectors have been used in experiments involving mice with immunity against the introduced virus. The results indicated that the exosome-protected virus did not cause immune reactions [19]. In addition, experiments have involved the introduction of such vectors into various tissues, such as nerve cells, particularly those in the inner ear [20, 21]. It means that the hybrid vectors can be safely introduced into different types of tissue, and the result is that they do not cause any severe immune reactions. However, the vectors have yet to be widely applied in CRISPR/Cas9 research, so this remains an opportunity for future studies.

Gold nanoparticles also promise to deliver gene drugs into tumor cells, though they should be further researched. Gold nanoparticles are a suitable drug delivery method because they are non-toxic, do not cause severe reactions, are stable, can inhibit bacteria, and can be modified to deliver substances into the cells [22]. Specifically, ligands can be added onto the gold nanoparticles for better recognition of cancer cells. For example, Wang et al. [23] have successfully introduced the CRISPR/Cas9 system into skin cancer cells using nanoparticles and liposomes. To deliver the plasmids to the cancer cells, they coated the gold nanoparticles with genetic material with positively charged liposomes [23]. These particles enter cancer cells and can release the drug when exposed to a laser; as a result of the intervention, the target gene (Plk-1) is knocked out, and the tumor is inhibited [23].

However, despite the successful experiment, scientists still claim that the challenge with gold nanoparticles lies in the accurate and efficient release of drugs at the target site, which will require further research [22]. Apart from previously discussed lasers, different stimuli have been studied concerning triggering the release of drugs

into the target cells. These have included internal and external stimuli [22]. However, the nanoparticles should be further modified to allow for a more efficient release of drugs into the target cells, which could be the focus of future studies.

Discussion: Clustered, regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) gene editing tool is a promising technique for cancer therapeutics. As many researchers have pointed out, its advantage lies in its efficiency and ease of design. It offers a possible solution to the treatment of cancer, which is why researchers in molecular biology need to direct their attention to the study of the current challenges associated with the implementation of the technique in clinical settings. The challenges have included the structure of the Cas protein and different ways of delivering it into cancerous cells. The research results show that non-viral delivery methods have fewer disadvantages, as they have greater packaging efficiency.

Furthermore, non-viral delivery vectors circumvent the immune reactions that could result from introducing viral vectors. Different modifications and ligands can be introduced on the surface of non-viral vectors to improve their recognition by the host and the specificity of some non-viral vectors. The study also indicates a need for investments in gold nanoparticle experiments, which possess several benefits in delivering CRISPR into the cells, including their high packaging efficiency and antimicrobial properties. However, the vector might be costly and will require investments.

Conclusion: This research paper has examined and highlighted several challenges, including the form and structure of the Cas nuclease, the types of engineering (in vivo vs. ex vivo), and the varieties of delivery methods. Different delivery methods appear efficient, including non-viral vectors, such as liposome-based particles, extracellular vesicles, hybrid vesicles, and gold nanoparticles. The delivery methods outlined in this research paper need further studies, and their side effects should be mitigated. Therefore, the delivery methods should be the focus of future studies.

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АҢДАТПА

ҚАТЕРЛІ ІСІК ТЕРАПИЯСЫНДА CRISPR/CAS9 ГЕНДІ ӨҢДЕУ ТЕХНОЛОГИЯСЫН ҚОЛДАНУДЫҢ ПЕРСПЕКТИВАЛАРЫ МЕН МӘСЕЛЕЛЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Қатерлі ісік Қазақстандағы өлімнің негізгі себептерінің бірі болып қала береді және CRISPR/Cas9 оны емдеудің ықтимал шешімдерін ұсынады. Кластерленген, тұрақты интервалды қысқа палиндромдық қайталанулар/CRISPR-байланысты протеин 9 (CRISPR/Cas9) – бөгде басқыншыларды жою үшін пайдаланатын жүйелі бактериялар. Бұл жүйе зерттеушілерге қатерлі ісік жасушаларының гендерін өңдеуге мүмкіндік беру арқылы қатерлі ісік терапиясы үшін перспективалы болып саналды.*

Жүйе көбірек сынақтарды қажет етеді, сондықтан студенттер мен әлеуетті инвесторлар үшін осы әдістеме туралы хабардар болу маңызды, сонымен қатар зерттеушілер үшін зерттеу мүмкіндіктері болуы мүмкін ағымдағы қиындықтарды атап өту маңызды.

Зерттеудің мақсаты *– зерттеу медициналық студенттер мен зерттеушілер үшін қатерлі ісік терапиясында CRISPR/Cas9 жүйесін қолданудың ағымдағы жағдайы туралы беделді ғылыми журналдардан ағымдағы ақпаратты талдауға және ұсынуға бағытталған. Бұл зерттеу жұмысы сондай-ақ Crispr/Cas9-ды онкологиялық ауруларды емдеуге арналған клиникалық жағдайларда енгізуге байланысты қиындықтарды көрсетеді.*

Әдістері: *Ғылыми әдебиеттер мен мәліметтер қорынан зерттеулер. (PubMed дерекқоры, Nature ғылыми журналы).*

Нәтижелері: *бұл зерттеу нәтижелері ғалымдардың Cas протеинінің түрлері мен құрылымын, сондай-ақ жеткізу әдістерін, соның ішінде вирустық емес жеткізу әдістерін (липосома негізіндегі бөлшектер, гибридті векторлар, алтын нанобөлшектері және жасушадан тыс) жақсартуға назар аударуы керек екенін көрсетеді. везикулалар) қатерлі ісік терапиясының қазіргі жағдайын жақсартуға ықпал ету.*

Қорытынды: *CRISPR/Cas9 - бұл әлі де қиындықтарға толы маңызды әдіс, оны зерттеу мүмкіндіктеріне айналдыру керек. Ағымдағы қиындықтарға Cas нуклеазасының нысаны мен құрылымы, инженерия түрлері (in vivo және ex vivo) және жеткізу әдістерінің сорттары кіреді. Жеткізу әдісінің әр түрінің өзіндік артықшылықтары мен кемшіліктері бар және одан әрі зерттеуді қажет етеді. Атап айтқанда, липосома негізіндегі бөлшектер, жасушадан тыс көпіршіктер, гибридті везикулалар және алтын нанобөлшектері сияқты вирустық емес векторлар болашақ зерттеулердің назарында болуы керек.*

Түйінді сөздер: *CRISPR, Cas9, қатерлі ісік, онкология, жеткізу векторлары, нанобөлшектер.*

АННОТАЦИЯ

ПЕРСПЕКТИВЫ И ПРОБЛЕМЫ РЕДАКТИРОВАНИЯ ГЕНОВ CRISPR/CAS9 В ТЕРАПИИ РАКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак остается одной из ведущих причин смертности в Казахстане, и CRISPR/Cas9 предлагает возможные решения для его лечения. Кластеризованные, регулярно чередующиеся короткие палиндромные повторы / CRISPR-ассоциированный белок 9 (CRISPR/Cas9) – это система, которую бактерии используют для расщепления чужеродных захватчиков. Система была признана многообещающей в отношении терапии рака, поскольку позволяет исследователям редактировать гены раковых клеток.*

Данная система требует дополнительных испытаний, поэтому важно повысить осведомленность студентов и потенциальных инвесторов об этой методике, а также привлечь внимание к текущим проблемам, которые могут стать исследовательскими возможностями.

Цель исследования *– проанализировать и предоставить актуальную информацию из авторитетных научных журналов о текущем статусе использования системы CRISPR/Cas9 в терапии рака студентам-медикам и исследователям. В этом исследовательском документе также освещаются проблемы, связанные с внедрением Crispr/Cas9 в клинических условиях для лечения рака.*

Методы: *Проведено исследование по научной литературе и базам данных (база данных PubMed, научный журнал Nature).*

Результаты: *Полученные результаты указывают, что ученым следует сосредоточиться на улучшении типов и структуры белка Cas, а также методов доставки, включая невирусные методы доставки (частицы на основе липосом, гибридные векторы, наночастицы золота и внеклеточные везикулы), чтобы способствовать улучшению текущего состояния средств для лечения рака.*

Заключение: *CRISPR / Cas9 – важный метод, который все еще сопряжен с трудностями, которые следует превратить в возможности для исследований. Текущие проблемы включают форму и структуру Cas-нуклеазы, типы инженерии (in vivo против ex vivo) и разнообразие методов доставки. Каждый вид способа доставки имеет свои плюсы и минусы и требует дальнейшего изучения. В частности, невирусные векторы, такие как частицы на основе липосом, внеклеточные везикулы, гибридные везикулы и наночастицы золота, должны быть в центре будущих исследований.*

Ключевые слова: *CRISPR, Cas9, рак, онкология, векторы доставки, наночастицы.*

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