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Application of CRISPR/Cas9 technique in non-small cell lung cancer

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Abstract: *CRISPR-Cas system, i. e. the adaptive immune system of bacteria and archaea, is a genome editing tool. Among them, CRISPR/CRISPR-related nuclease 9(CRISPR/Cas9) is most used to explore cancer-related drug targets and gene pathways, helping researchers to accelerate research on cancer. Non-small cell lung cancer (NSCLC) is one of the most common lung cancers, but there are still some deficiencies in the related treatments. This article mainly reviews the application of CRISPR/Cas9 in NSCLC in recent years, including drug targets, mutation models, gene and pathway screening, as well as its emerging applications in drug resistance and other aspects, to provide reference for the research of NSCLC.*

Keywords: *CRISPR/Cas9, NSCLC, gene editing*

1. Introduction

CRISPR-Cas system, that is, the adaptive immune system of bacteria and archaea, is an adaptive immune system unique to prokaryotes, which can resist the invasion of plasmids and virus particles [1], and can accurately target and edit certain gene mutations that initiate the growth and spread of cancer cells [2]. CRISPR-Cas is composed of two parts, namely, CRISPR array and Cas proteins. CRISPR array consists of clusters of short palindromes with regular intervals, and Cas proteins are CRISPR-related proteins [3]. The CRISPR-Cas system is a genome editing tool that undergoes three processes: within bacterial cells, microorganisms integrate detected exogenous genetic material into their genomic CRISPR arrays, a process broadly referred to as adaptation; Subsequently, CRISP array transcription produced CRISP-RNA (CR RNA), and Cas protein transcription produced CAS (effector nuclease). The two combined and expressed after a series of processing and assembly into different monitoring complexes, producing specificity. These different monitoring complexes constitute a Cas-effector nuclease that mediates target interference or cleaves a single large RNA, leading to target interference and adaptive immunity [4]. According to the difference in Cas components, CRISPR-Cas systems can be divided into two types. One type is a multi-subunit effector that contains multiple Cas proteins, and the other type is an effector that consists of a single, large, and multi-domain protein [3]. According to the classification based on the use of different ribonucleoprotein (RNP) complexes, CRISPR-Cas system mainly includes five types: Cas1, Cas2, Cas3, Cas9 and Cas10. In addition, there are some new systems being introduced, such as Cas12, Cas13 and Cas14n.

CRISPR-Cas technology has new applications in various fields. Introducing a specific DNA modification into the complementary DNA strand of crRNA of CRISPR-Cas12a to temporarily inactivate Cas12a, whereby various DNA glycosylases can be selectively detected [5]; Using CRISPR/Cas12a to mediate plant MicroRNA knockout is more effective than Cas9 and is of great help in regulating grain quality and seed development [6]. Using CRISPR-Cas technology to develop a tool for exploring the mechanism and functional modification of probiotics [7] has played a significant role in the field of food health. The RPA-based CRISPR/Cas12a detection combined with lateral chromatography detection method can quickly detect Shigella flexneri in food samples, providing a simple, rapid and effective method for monitoring food and drug safety [8]. The CRISPR/Cas13 system is widely used in basic and applied science [9]. The gene circuit of CRISPR/Cas13d and crRNA hybridization (MONARCH) pushes

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the RNA-guided RNA cleavage system to the forefront as an easy-to-use programmable tool for transcriptome engineering in biotechnology and medical applications [10]. In addition to the above-mentioned applications, Cas9 is the most commonly used genome editing tool, and cas9 has received the most research by researchers [11].

Lung cancer is one of the most common malignant tumors affecting human health and the largest cause of cancer death worldwide. In 2022, there were nearly 2.5 million new cases of lung cancer worldwide, accounting for 12.4% of all cancers in the world [12]. Non-small cell lung cancer (NSCLC) is one of the most common subtypes of lung cancer, and accounts for 85% of the overall incidence of lung cancer [13]. Common treatment methods usually include surgery, radiotherapy, chemotherapy, molecular targeted therapy, etc. The survival rate of patients with non-small cell lung cancer treated by traditional radiotherapy or chemotherapy is low, and targeted therapy has brought a new dawn for the treatment of non-small cell lung cancer. The traditional NSCLC targets include EGFR, TKI, and ROS1 [14–16]. However, up to now, about one-third of the patients are still unable to determine the driver gene or the related pathway, resulting in no suitable treatment plan for these patients [17]. The application of gene editing technology to find or screen out the appropriate related pathways or targets, and models will be of great help for the treatment of patients with NSCLC.

Before the application of CRISPR to cancer treatment, gene editing was usually performed with zinc finger nuclease (ZFN) and transcriptional activator factor-like effector nuclease (TALEN), but both methods relied heavily on the protein engineering of DNA binding domains to recognize and edit specific DNA sequences, and the emergence of CRISPR/Cas9 system solved these problems. Compared with single-stranded RNA (sgRNA) targeting genomic sequences, which has greater flexibility and efficiency, CRISPR/Cas9 technology has completely changed the biological field [18,19].

CRISPR/Cas9 belongs to the second class of CRISP system [20]. Research results in cell and animal models have shown that CRISP/CaS9 technology can effectively treat cancer. This paper mainly discusses the screening of targets, mutation models, genes and pathways, the application in cell resistance and other emerging applications of CRISPR/Cas9 technology in non-small cell lung cancer.

2. Applications

2.1 Screening of targets

Identifying new targets is particularly important for the development of drugs to treat NSCLC, and CRISPR-mediated gene editing has identified many new therapeutic targets in cancer. China researcher Wang Qianqian et al. performed genome-wide CRISPR/Cas9 screening in two NSCLC cell lines harboring wild-type TP53 and receptor tyrosine kinase (wtTP53-RTK) genes using the GeCKO v2.0 lentivirus library, and the screening results confirmed that MDM2 was a potential therapeutic target of wtTP53-RTK NSCLC. The selective MDM2 inhibitor RG7388 has significant tumor inhibition when used alone or in combination with pemetrexed for the treatment of this subtype of nsclc, but it has a poor therapeutic effect on other subtypes of nsclc [17].

The PAICS gene was selected by genome-wide CRISPR/Cas9 screening in the H460, H1299, and A549 cell lines containing wild-type EGFR genes, as well as in the BEAS-2B cell line as a control. The role of the PAICCs gene in NSCLC cell proliferation was investigated to validate the screening results, which showed that the expression of PAICCs was up regulated in NSCLC tissue samples, especially related to the progression of NSCLC, and in addition, the increased level of PAICCs was significantly associated with poor OS in NSCLC patients. ShRNA-mediated PAICS knockdown significantly inhibits the activity and proliferation of EGFR wild-type NSCLC cells and induces apoptosis [21]. This study successfully identified PAICS as a potential therapeutic target for EGFR wild-type NSCLC that could promote apoptosis of EGFR wild-type NSCLC cells by knocking out PAICS to induce DNA damage.

The whole genome CRISPR/Cas9 is used to screen a survival gene heat shock protein family D member 1 (HSPD1 or HSP60) that is related to the poor prognosis of NSCLC patients and is commonly expressed in NSCLC, and a series of studies have proved that the targeted anti-cancer effect of HSPD1 depends on oxidative phosphorylation and the verified molecular determinants of KHS101 sensitivity, highlighting the importance of mitochondrial metabolism in the development of anti-NSCLC drugs and HSPD1 as a target in the improvement of NSCLC [22].

In addition to the above screened targets, many researchers have screened out many special targets. A transmembrane receptor procalcitonin 7 (PCDH7) is often overexpressed in lung adenocarcinoma.

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Researchers have established a transgenic mouse model using CRISPR/Cas9 technology and determined that PCDH7 is an effective lung cancer driver and operable therapeutic target. Its expression can significantly accelerate the occurrence of lung cancer caused by KrasG12D and enhance the activation of MAPK pathway [23]. Li Fei et al. performed mixed epigenomic-wide CRISPR knockout screening in vitro and in vivo, and identified histone chaperone nuclear phosphoprotein 1 (Npm1) as a potential therapeutic target [24], while Nicholas Dompe et al. identified the MAPK7 target, which is very promising for combination with MEK inhibitors [25]. These targets screened by CRISPR/Cas9 have provided new treatment ideas for patients with NSCLC and a new direction for the development of new drugs. Subsequent researchers can use CRISPR/Cas9 technology to screen out more useful targets and provide more reference paths for future research on NSCLC.

2.2 Screening of mutation model

The development of mutant models is a strategy for the treatment of non-small cell lung cancer, and the CRISPR/Cas9 technique has been demonstrated to be feasible for screening transplantation models of virtually any cell line or genetic background. Foreign scholars have generated a mouse model of myeloid malignant tumor using CRISPR/Cas9 genome editing. After a series of studies, it is finally concluded that Cas9 genome editing is conducive to the design of a broader range of in vivo cancer models to better reflect the complexity of human diseases [26]. It can be speculated that CRISPR/Cas9 technology can be applied to the screening of mutation models of NSCLC.

Researchers such as Chen Sidi extracted and cloned a cell line (designated as KPD) containing oncogenic Kras as well as homozygous p53 and heterozygous Dicer1 from mouse non-small cell lung cancer, and transduced the cell line with a lentivirus carrying a Cas9 transgene and fused with green fluorescent protein (GFP) to generate a clonal cell line (Cas9-GFP KPD). The cell line was transduced with the lentivirus of a mixed genome-wide mouse sgRNA library (mGeCKOa) to obtain a pool of mutant cells, which was then infected with the mouse and sequenced. The results showed that CRISPR/Cas9-mediated mutagenesis could promote metastasis. In combination with other research results, it was concluded that this study provided a roadmap for screening Cas9 in vivo, and the model could be used in future studies to explore other homeotypes, delivery methods or target organs for metastasis [27].

2.3 Screening of genes and pathways

The unbiased whole-genome genetic screening for loss of function using Crispr-Cas9 in a group of NSCLC cells stably transfected with the five KRAS G12C mutations expressing CaS9 identified several novel pathways, such as YAP, CUL5-SOCS3, SAGA, and mediator complex, as well as mitochondrial respiratory pathway that was identified as an important rescue factor in the KRAS G12C/KEAP1 co-mutated cells [28].

Genome-wide CRISPR/Cas9 screening of the KRAS/STK11 mutant NSCLC cell line identified recurrent, potentially targeted synthetic lethal (SL) genes and other potentially targeted genes and pathways, such as the YAP/TAZ/TEAD pathway. The siRNA/shRNA assay confirmed several SL genes and validated the YAP/TAZ/TEAD pathway in vitro, demonstrating the correlation of screening results. The results showed that the synthetic lethality of DNA damage genes indicated that there might be synergistic effects between G12C inhibitor and some conventional chemotherapy drugs, and the expression of some genes in G12C inhibitor resistance samples was increased [29]. Future studies may explore the utility of the selected genes and pathways in combination with G12C inhibitors.

2.4 The application in cell resistance

Traditional methods such as chemotherapy, radiotherapy and surgical resection are usually considered as the first-line treatment, and drug resistance is easily generated when traditional methods are used to treat NSCLC. The reasons for the generation of drug resistance are complex and variable, and epithelial-mesenchymal transition (EMT) is one of the reasons [30,31]. Johan Vad-Nielsen et al. adopted a histological method to analyze acquired EMT-related EGFR TKI resistance (EMT-E-TKI-R), and then used CRISPR/Cas9 to perform functional examination on the key findings of the histological analysis, in order to confirm the importance of MIR141/MIR200C-ZEB1/ZEB2-FGFR1 in NSCLC cell EMT-E-TKI-R [32].

In addition, researchers have knocked in three different known resistance mutations in ROS1+patient-derived cell lines, causing resistance in endogenous translocated ROS1 alleles using CRISPR/Cas9,

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building NGR indices calculated by live cell imaging, performing pharmacological assays in 2D and 3D cell cultures, and concluding that spheroids are more sensitive to TKI than monolayers, an innovative approach that accurately defines the effects of emerging TKI resistant variants and ultimately facilitates drug development in a Qualcomm-scale fashion. Importantly, as the CRISPR/Cas9 technology improves the modeling of other genetic variations, the results of this experiment can be applied to a wider range of malignant tumors facing therapeutic resistance [33].

The redox regulator NRF2 is over-activated in the NSCLC quilt, resulting in resistance to chemotherapy and radiotherapy. Researchers used CRISPR/Cas9 to conduct negative selection screening against the oxidase gene to determine the redox vulnerability of the KEAP1/NRF2 mutant NSCLC. Several important hits, including pentose phosphate pathway, thioredoxin-dependent antioxidant system, glutathione reductase, and mitochondrial superoxide dismutase 2 (SOD2), were identified through screening. In particular, SOD2 was emphasized as a unique antioxidant enzyme with the potential for therapeutic intervention in NSCLC to find a solution to drug resistance [34].

In addition, CRISPR/Cas9-bound RNA is a fast and accurate genome editing technology. Researchers such as Yang Y used CRISPR/Cas9-bound RNA genome editing technology to knock out ABCB1, inhibit multi-drug resistance (MDR) in cancer cells, or reverse ABCB1-mediated MDR in cancer cells, significantly enhancing the sensitivity of chemotherapeutic drugs, and providing a useful value for conquering cancer multi-drug resistance [35].

2.5 Other emerging applications

In addition to screening for targets, pathways, or models, the CRISPR/Cas9 system can also be used to target the EGFR point mutation L858R commonly found in NSCLC, using oligonucleotide-guided recognition of L858R as a pro-spacer adjacent motif (PAM) sequence suitable for DNA cleavage. This targeting method can specifically target cancer-defining mutations to distinguish changes in individual nucleotides [36].

EML4-ALK rearrangement is an important biomarker that plays a key role in the treatment decision of patients with non-small cell lung cancer [37,38]. The various NSCLC cell lines containing EML4-ALK rearrangement variants 1, 2, and 3a/b were edited with CRISPR/Cas9 and then xenotransplanted, with the obtained tumor serving as a candidate reference substance for the detection of multiple EML4-ALK rearrangements [39,40].

Using CRISPR/Cas9 technology and specific DNA bar code, some foreign scholars have designed a CRISPR bar code to summarize and track the emergence of cancer cell subsets containing target mutations, using this method to simulate the different mechanisms of EGFR inhibitor resistance of lung cancer cells and evaluate the effect of combined drug therapy. In addition, most types of genetic modifications can be studied. Compared with virus libraries, CRISPR bar codes are much faster and easier to implement for tracking cell heterogeneity, and are simple and flexible, which should greatly promote the functional study of specific mutations [41].

In addition, an innovative method for the treatment of non-small cell lung cancer was proposed in 2022, which causes collateral damage in the form of CRISPR-mediated exon skip and destroys nuclear factor erythroid 2-related factor 2 (NRF2) to improve or restore chemotherapy sensitivity [42]. CRISPR/Cas9 can also be used to precisely destroy the allele of the carcinogenic mutant EGFR with high specificity to induce effective tumor regression [43].

3. Conclusion

As a gene editing tool, CRISPR/Cas9 is cheap and efficient, but its accuracy and selectivity are very important to it. Although its loci are specific, the CRISPR/Cas9 system may have up to six mismatches in complementary sgRNA sequences, which will bring a lot of inconvenience to future research. However, further research shows that although mismatches will reduce the catalytic activity of Cas9/sgRNA complex, different mismatch positions will affect the operating efficiency. The operation efficiency of Cas9 is mainly affected by the conformational changes of Cas9 and the mutual arrangement of sgRNA and substrate [44]. Therefore, it is very important to correctly select the target sequence when using CRISPR/Cas9 to prevent it from cutting similar sequences and improve the accuracy.

NSCLC seriously affects people's health all over the world, making many patients miserable and many families ruined. Many patients were found to be in the late stage and missed the best time for

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treatment. Using CRISPR technology can help some patients quickly screen targets, mutant models or inhibit pathways, or use other emerging technologies to provide great help for the treatment of NSCLC patients. CRISPR technology, especially CRISPR/Cas9, offers new prospects for designing more effective and personalized cancer treatment regimens and has a positive impact on cancer research, with great potential in so many fields. In future research in many fields, CRISPR-Cas technology can be used to achieve unexpected results.

Author's contribution

Lihua Qin inquired about the literature and wrote the first draft of the article, Shu Zhang revised the article, Xiaoqun Duan and Tingchun Wang provided ideas for the article. All the authors carefully examined the manuscript and approved the final manuscript.

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