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Research on the gene therapy and prevention of lung cancer

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Abstract. In recent years, there have been significant advancements in molecular biology, gene therapy technology, and high-tech testing techniques. As our understanding of the pathogenesis of lung cancer continues to deepen, it has become evident that gene therapy plays a crucial role in its treatment. This article provides an overview of tumor cell development, various gene therapy techniques including suicide gene therapy, silent gene therapy, cancer suppressor genetic therapy, and antibody genetic therapy. Additionally, it analyzes the application value, treatment technology, and safety concerns associated with gene therapy. The discussion also covers the safety issues and current application status of viral and nonviral vectors in gene therapy, comparing the advantages and disadvantages of different vector types. Furthermore, the article summarizes the future directions for designing and improving gene delivery vectors, along with their clinical application prospects. Ultimately, this article offers insights into the significance and treatment approaches for early prevention of lung cancer.

Keywords: gene therapy, delivery vectors, tumor therapy, P53 gene, lung cancer prevention.

1. Introduction

The incidence of cancer in China continues to rise, and achieving a breakthrough in the five-year survival rate has been a persistent challenge. With the continuous development of gene biological therapy, it also has a very important impact on the treatment of cancer. However, the pathogenesis of lung cancer is very complex, and the specific genes involved require further exploration. There is a lack of an ideal gene vector that can safely and efficiently transfer genetic material, integrate it into the target genome, and ensure long-term expression in cells. Viral vectors have high transfection efficiency, but pose safety risks such as carcinogenesis and mutation. Although nonviral vectors have no cytotoxicity or immunogenicity and are relatively simple to prepare, their transfection efficiency is relatively low. Therefore, we can optimize the selection of target genes and continuously explore and improve the efficiency, safety, and accuracy of gene delivery vectors [1]. Cancer is a genetic disease involving changes in genetic information between tumor cells and normal cells. This leads to the activation of oncogenes and inactivation of tumor suppressor genes, resulting in excessive cell proliferation and tumor formation. This provides a theoretical basis for gene therapy for lung cancer. Therefore, understanding gene therapy for lung cancer confirms its significant role in cancer treatment and promising future prospects. [2]. This article will discuss the trend of gene therapy for lung cancer, the occurrence and development process of tumor cells, the methods and delivery pathways of gene therapy.

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2. The treatment methods for tumors

In China, lung cancer is currently one of the most common cancers, second only to gastric cancer and liver cancer. The incidence rate is increasing year by year, and the five-year survival rate is less than 15%. How to further improve the treatment effect has always been an important research direction. In recent years, with the continuous development and improvement of molecular biology and gene therapy technology, as well as the deepening understanding of the pathogenesis of lung cancer, it has been confirmed that gene therapy plays a very important role in the treatment process of lung cancer.

The occurrence and development of lung cancer involve a long-term, multi-step, multi-gene process, including apoptosis disorders, oncogene activation, tumor suppressor gene inactivation, and gene mutations. Apoptosis refers to the autonomous and orderly death of cells controlled by genes to maintain the stability of the internal environment. Apoptosis and cell necrosis are distinct processes in cellular biology. While apoptosis is an active process involving the activation, expression, and regulation of specific genes, cell necrosis is a passive phenomenon that occurs under pathological conditions. It is not a phenomenon of self-injury under pathological conditions, but a death process that actively strives to better adapt to the living environment. The signals that trigger apoptosis can be categorized into two types: extracellular signals mediated by receptors and endogenous signals mediated by mitochondria. Furthermore, apoptosis can be further classified into exogenous and endogenous apoptosis, which are regulated through different apoptotic signaling pathways and mechanisms [3].

The inactivation of tumor suppressor genes can be addressed through gene therapy, which involves introducing wild-type tumor suppressor genes into target cells. This approach serves to replace the inactivated tumor suppressor genes and restore the normal growth phenotype of cells. Additionally, it can induce apoptosis in tumor cells, thereby contributing to the treatment of tumors. P53 is currently the most mutated gene in lung cancer, and introducing wild-type P53 genes has become an essential method in gene therapy for lung cancer treatment [4].

A suicide gene refers to the introduction of some viral or bacterial genes into target cells, and the enzymes it expresses can catalyze the conversion of non-toxic drug precursors into cytotoxic substances, thus leading to the killing of receptor cells carrying the gene. At the same time, it can also achieve selective in situ transduction and specific killing, avoiding the multiple steps involved in the application of in vitro gene therapy, the difficulty of obtaining and cultivating target cells, the process of target gene transduction, screening, and reinfusion, making it one of the early gene therapy methods to enter clinical practice. At present, there are many systematic methods for suicide gene therapy, such as Herpes simplex virus type 1 thymidine kinase (HSV-TK), escherichia coli Cytosine deaminase (CD), purine nucleotide phosphorylase (PNP) Escherichia coli nitroreductase gene system, Carboxypeptidase A Carboxypeptidase G2 gene system and Horseradish peroxidase gene system, but the suicide gene therapy systems with the most research applications are HSV-TK and CD [5].

Cancer, like other tumors, is a vascular dependent tumor. Factors that inhibit angiogenesis include endostatin, angiostatin, and interferon- α. The mechanism of this method is based on the difference of gene expression between tumor and normal endothelial cells, thus selectively inhibiting the expression of abnormal genes in tumor endothelial cells, inhibiting tumor angiogenesis, and achieving the purpose of tumor treatment. At present, the strongest known angiogenic cytokine is VEGF, and people are working on the study of antagonizing VEGF/VEGFR against angiogenesis. Antisense nucleic acids, soluble VEGFR, ribozyme, anti-VECF monoclonal antibodies, and Receptor tyrosine kinase (RTK) inhibitors have been used in gene therapy against tumor angiogenesis.

Antisense nucleic acid technology designed for abnormal activation of oncogenes in tumor cells can effectively regulate gene expression in cancer cells. Its therapeutic target genes include oncogenes, growth factors and their receptors, cell signal transduction systems, cell cycle regulators, enzymes, etc. In vitro experiments using antisense oligonucleotides can inhibit various oncogenes, such as c-myb, c-myc, K-ras, c-H-ras genes, etc.

Therefore, the antonym's K-RAS gene is transferred to the possibility of cancer cell proliferation and tumors in lung cancer cells with mutations in K-RAS gene mutations. Some studies have also shown

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that the use of anti-K-ras adenovirus vectors has successfully inhibited the growth of lung cancer xenografts.

Modified genes refer to genes that have or do not have any phenotypic effects and are present simultaneously with another mutated gene, which can affect the degree of expression of another gene. If it has the same phenotypic effect, it is not different from the cumulative gene. The tolerance demonstrated by patients during the conventional tumor treatment stage has a significant impact on the efficacy, and it is also important to protect normal tissues during the treatment process. The most common side effects of radiotherapy and chemotherapy for lung cancer are radiation pneumonia and Bone marrow suppression. Therefore, gene therapy can be used to modify normal cells, such as transfecting multidrug resistance gene (MDR) into hematopoietic stem cells of tumor patients to make them more resistant to chemotherapy drugs for tumor cells, so as to improve the chemotherapy dose during the treatment process, shorten the interval of drug use, and reduce Bone marrow suppression [6].

3. Gene therapy vectors

The most basic problem of gene therapy is to efficiently introduce target genes, i.e., exogenous normal genes, into target cells and express them effectively, in order to correct or compensate for diseases caused by gene defects and abnormalities, and thus achieve the therapeutic goal. Common methods for gene introduction include virus transfection, liposome fusion, ligand membrane receptor binding, gene gun, microinjection, and other methods. The most commonly used gene metastasis in the treatment of lung cancer is the internal injection of the target gene and the carrier. The carriers used for lung cancer gene therapy mainly fall into two types: viral vectors and non-viral vectors.

3.1. Classification and advantages and disadvantages of virus vectors

Common viral vectors include adenovirus, Adeno-associated virus, retrovirus, lentivirus, etc. Retroviruses have low toxicity, high transfection efficiency, and long-term stable expression of target genes. However, they carry a certain risk of carcinogenesis, which may lead to the activation and mutation of tumor suppressor genes. Currently, they are only suitable for in vitro cell infections due to their packaging capacity of less than 8 kb of foreign genes.

At present, retroviral vectors have been widely studied in cancer treatment. Although traditional chemotherapy methods can effectively inhibit the growth of cancer cells and control the condition, they also cause significant damage to the patient's body. Therefore, retroviruses have great application prospects for killing cancer cells at the molecular level.

Adenoviruses are non-enveloped particles with double-stranded circular DNA molecules inside their capsid. Its advantage is that it can infect the respiratory tract, gastrointestinal tract, urethra, bladder, eyes, liver, etc., making it suitable for gene delivery in multiple tissue cells. They are relatively safe as they lack an envelope and are not easily inactivated by the body's own complement. Therefore, it has a greater effect on gene delivery in the body. However, they cannot be stably expressed in rapidly dividing cells for a long time. If multiple infections are repeated to achieve repair, the body will produce more immune responses, affecting gene expression and treatment effectiveness. Labeling

Adenovirus vectors in tumor cells allows tracing and microscopic observation of the virus transportation from the cell surface to the intracellular space, facilitating the study of virus infection processes. Adenovirus labeling methods include non-genetic markers, which use chemiluminescence groups to label mature virus particles, and genetic markers, which use fluorescent proteins to mark the capsid protein and core protein of adenovirus. Virus labeling plays a significant role in the selection of gene therapy vectors [8].

Adeno-associated virus (AAV) is a single-stranded DNA virus that requires a helper virus (usually adenovirus) for replication. Its advantage is that its structure is relatively simple, ,allowing foreign genes to be stably integrated into the host cell's chromosomes. Adeno-associated viruses have no pathogenicity for host cells and can be stably expressed in a variety of tissues and cells for a long time. However, similar to retroviruses, the small capacity of exogenous genes also affects the therapeutic effect.

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The lentivirus vector is a gene therapy vector developed based on HIV-1 (human immunodeficiency virus type I). The difference between ordinary retroviral vectors is that they have the ability to infect both dividing and non-dividing cells, while also infecting a wide range of hosts. In addition, compared with adenovirus and Adeno-associated virus, lentivirus has a larger capacity and can carry a larger and more complex genome, integrate and deliver it to host cells and stably express it for a long time. Lentivirus is generally not used in vivo because of its poor transfection effect in vivo. However, lentiviral vectors can be used to treat RNA interference, suicide genes and immune genes. RNAi mediated by lentiviruses specifically blocks or suppresses gene expression through the mediation of double stranded RNA. Lentivirus-mediated RNAi combines the specificity of Lentivirus vector and RNAi to inhibit the expression of Homeotic genes and continuously and stably induce the silencing of target genes. Meanwhile, structural and functional abnormalities in genes such as growth factors and their receptors, signal transduction factors, and nuclear gene transcription are all related to the occurrence and development of tumors. Lentivirus-mediated RNA interference specifically blocks or suppresses gene expression through the mediation of double-stranded RNA. At present, RNAi has made significant breakthroughs in silencing mutated genes and enhancing anti-tumor drugs. It is widely used in various malignant tumors, including nasopharyngeal carcinoma, cervical cancer, osteosarcoma, leukemia, and liver cancer [9].

3.2. Classification and advantages and disadvantages of non-viral vectors

Non-viral carriers include cationic polymer carriers, liposome, and nanoparticle carriers.

Liposomes are composed lipid bilayers with hydrophilic and hydrophobic groups. Liposomes encapsulate foreign genes and fuse with the cell membrane, thereby allowing foreign genes to enter the cell. The transfection method is simple, non-immunogenic, and has low cytotoxicity, making it effective in gene therapy for lung cancer. Cationic polymer carriers bind with anionic rich DNA to form a complex that adheres and integrates onto the surface of the cell membrane, and is then internalized by the cell membrane.

Nanoparticle carriers have no significant impact on cell growth and activity within a certain range of particle numbers and have almost no cytotoxicity. At the same time, they also lack immunogenicity and do not cause cells to produce immune responses. However, compared to liposomes, nanomaterials have a higher efficiency in exogenous gene transduction, and their own volume is small, which can reach various tissues throughout the body with the blood. They have great potential for in vivo gene therapy [10].

4. Discussion

During genetic tumor treatment, designing nucleic acid sequences to target abnormal genes in cancer cells can effectively induce cell apoptosis or promote immunogenicity. Targeting carriers to tumor cells is crucial for maximizing drug delivery to cancer cells and avoiding off-target effects. Both viral and non-viral vectors have their advantages and disadvantages. Viral vectors have high transfection efficiency but carry safety risks and a potential for mutation. Non-viral vector delivery is more efficient and less cytotoxic, but transfection efficiency still needs improvement. Therefore, future directions should prioritize delivery vector categories with high transfection efficiency, low cytotoxicity, and safety and reliability.

Although the continuous development of new treatment methods such as biological therapy, radiation therapy, and chemotherapy has provided more possibilities for the treatment of lung cancer, most patients have advanced cancer cells at the time of medical treatment, and their 5-year survival rate has not been significantly improved. Therefore, early prevention of lung cancer is particularly important.

Promoting awareness of the harmful effects of smoking and advocating for non-smoking or smoking cessation are important measures. By controlling air pollution, strengthening environmental hygiene, reducing occupational exposure and air pollution, we can control the incidence of lung cancer.

Actively prevent and treat chronic lung diseases, such as chronic bronchitis and tuberculosis.

Conducting relevant lung cancer tissue surveys for individuals over 40 years old with a history of heavy smoking, high-risk occupational groups, and high-risk areas is important. Through publicity and education, especially for smokers over 40 years old who have symptoms such as an unexplained cough and blood in their sputum, they should seek medical attention in a timely manner and receive early detection and treatment [11].

5. Conclusion

Gene therapy is an efficient treatment method for various malignant diseases, including cancer, and offers precise prevention of related diseases. The essence of gene therapy is to transfer target genes into cells through vectors for treatment, so the delivery effect of genes becomes even more crucial. During genetic tumor treatment, the continuous design and improvement of nucleic acid sequences can effectively induce apoptosis in tumor cells. At the same time, it is necessary to consider the targeting of the carrier to tumor cells to avoid cell off target effects. When selecting viral and non-viral vectors, their respective advantages and disadvantages should be taken into account. Viral vectors have high transfection efficiency but carry safety risks, while non-viral vectors are less cytotoxic but require improved efficiency. Therefore, the future direction should prioritize delivery vector categories with high transfection efficiency, low cytotoxicity, and safety and reliability.

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