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Application of inorganic nanomaterials for drug delivery in lung cancer

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Abstract. Lung cancer has been one of the most common cancers in the world for more than 100 years and has taken many people's lives. Many people suffer from lung cancer due to smoking, second-hand smoke, and serious air pollution or pollutant gathering environment. It is necessary to find a good medical solution. Compared with traditional chemotherapy and immunotherapy, targeted therapy has more advantages in the impact on patients and the efficiency of treatment. How to develop targeted therapeutic drugs has become a topic, and nanoscale targeted drugs have become the most appropriate choice. Among them, there are many inorganics suitable for nano-targeted drugs and nano-drug carriers, such as metals, metal oxides, and non-metals. By blocking the genetic material in lung cancer cells, it can avoid the division and differentiation of lung cancer cells, so as to achieve the purpose of treating lung cancer. This review will focus on the above three kinds of nano-targeted drugs, and discuss their therapeutic principles, drug delivery, activation mode, and biotoxicity.

Keywords: lung cancer, nanomedicine, inorganic material.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide, and it is widespread. About six percent of people will be diagnosed with lung cancer in their lifetime, and it causes about 120,000 deaths in the United States each year. Lung cancer originates in the lungs and may spread to various organs or lymph nodes throughout the body. Similarly, cancer from other organs may spread to the lungs. In general, lung cancer can be divided into two major groups based on the different growth patterns of lung cancer: small-cell carcinoma and non-small-cell carcinoma. Non-small cell lung cancer is more common than small cell lung cancer. The main causes of lung cancer include smoking, secondhand smoke, and radon, and people living in areas with high levels of air pollution have a significantly increased risk of lung cancer, especially in workplaces that contain chemicals such as asbestos, arsenic, and chromium.

There are three main treatments for lung cancer: chemotherapy, targeted therapy, and immunotherapy. The early treatment of lung cancer was chemotherapy. However, after entering the 21st century, chemotherapy has strong side effects on the body due to its effect on healthy cells in the body, and immunotherapy has a low objective response rate, so after the 21 century, targeted therapy gradually emerged, and practical application of targeted therapy and immunotherapy is gradually increasing. Major limitations of conventional drugs include adverse effects, unspecificity, poor bioavailability, and difficulty to dosing control dosing. Compared to conventional drugs, nanoscale targeted therapy has

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unique advantages, such as low biological toxicity, easy-to-control bioavailability, avoiding the accumulation of drugs in non-lesion areas, accurately controlled drug release, and improving pharmacokinetics, thereby reducing the harm of side effects to the human body [1].

These advantages can be helpful in the detection, diagnosis, and treatment of lung cancer. Nanomedicine can be classified into organic nanomedicine, inorganic nanomedicine, and nano gel, which is composed of inorganic and organic substances. Among them, there are hidden dangers in the stability of organic nanomedicines, which may lead to the early release of drugs, thus losing the significance of precisely targeted therapy of nanomedicines. Compared with organic nanomedicines, inorganic nanomedicines have advantages in stability. Common inorganic materials, such as metal nanoparticles (NPs), nanoscale metal oxides, and non-metallic nanomaterial can be used as nano-targeted drugs or nano-drug carriers. Here, the principles, drug delivery, and advantages and disadvantages of the above inorganic nanomedicine in the treatment of lung cancer will be introduced.

2. Metal NPs

Gold nanoparticles (Au-NPs), as the most commonly used metal for targeted drug delivery, are important in the application of lung cancer treatment. The properties of Au-NPs and their modifiability and functionality facilitate the assembly of oligonucleotides and proteins and play a good role in diagnosis and imaging. To control the volume and surface function of gold nanoparticles, there was a precedent of treating hydrogen tetrachloroaurate ($HAuCl_4$) by boiling water and citric acid as early as 1951, and the size of the particles could be controlled by controlling the proportion of reactants. In 1994, more stable gold nanoparticles protected by alkyl thiol were prepared by means of two-phase reduction. Gold nanoparticles can avoid reaggregation in solution by the combined action of strong sulfhydryl-gold interaction and van der Waals forces [2].

Au-NPs have advantages in optoelectronic properties, specific surface area, biocompatibility, and biotoxicity. However, it is worth mentioning that both the toxicity and cellular uptake of Au-NPs are closely related to particle size. Studies have shown that the inhibitory effect of 5 nm Au-NPs on lung cancer cell lines A549 and 95D can be demonstrated at 48 h and 72 h, respectively. Gold nanoparticles with diameters of 10 nm, 20 nm, and 40 nm had little effect on the growth and proliferation of A549cell and 95D cells. There are studies showing that intercellular adhesion molecule-1 (ICAM-1) and matrix metalloproteinase 9 (MMP-9) are considered markers for the detection of lung cancer due to their characteristics of involvement in cancer cell invasion and migration. According to the detection of ICAM-1, the mRNA expression of ICAM-1 was significantly increased under the action of 5nm and 10nm Au-NPs, and the mRNA expression of MMP-9 was also increased under the action of 5nm AUNPs. By western blotting, the expression of MMP-9 and ICAM-1 in A549 and 95D cell lysates increased significantly after treatment with 5 and 10 nm gold nanoparticles but decreased significantly after treatment with 40 nm gold nanoparticles. It can be concluded that the diameter of gold nanoparticles can regulate such protein substances. Au-NPs with a diameter of 5 nm exhibited both anti-proliferation and pro-proliferation effects, and their cores were benign and non-cytotoxic. Au-NPs with diameters of 20 and 40 nm promoted cell proliferation in A549 cells, but not in 59D cells. This proves that the effect of gold nanoparticles on cells is not universal. Both MMP-9 and ICAM-1 play a certain role in the spread of cancer, and the inhibition of MMP-9 expression is positively correlated with the inhibition of cancer cell migration. With the enhancement of ICAM-1 expression, cancer cell apoptosis will also be enhanced. Compared with other Au-NPs, Au-NPs with a diameter of 5 nm were found to be effective in inhibiting cell proliferation, promoting cell apoptosis and enhancing cell invasion in A549 cells [3]. It has been shown that gold nanoparticles alone added to A549 cells do not express cytotoxicity. But in certain cases, for example, L-buthionine sulfoximine (BSO) inhibits intracellular glutathione (GSH), and the cytotoxicity of gold nanoparticles is significantly expressed. Among them, GSH is a ubiquitous antioxidant in most organisms, which can protect cells from reactive oxygen species, heavy metals, free radicals and other substances to damage cells. Some studies have compared the effect of BSO and gold nanoparticles on the inhibition of cell growth. The inhibition degree of cells treated with gold nanoparticles and BSO was slightly higher than that of cells treated with BSO alone. According to the

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morphological analysis, the cells treated with gold nanoparticles and BSO together appeared to become round and shrink in morphology, while the cells treated with gold nanoparticles or BSO alone did not show any significant changes. This suggests that gold nanoparticles may cause cell death when the GSH content in cells is low, which is a biotoxicity problem to be considered in drug delivery. However, the above experiments also suggest that GSH can prevent the cells from being induced by gold nanoparticles and thus prevent cell death. When gold nanoparticles, BSO and GSH were simultaneously added into the cells, it was observed that the cells did not die, and the inhibition of cell proliferation was reversed after the continued addition of GSH, indicating that GSH could help the cells to relieve the toxicity of gold nanoparticles. Therefore, the gold nanoparticles were pretreated with GSH to reduce the biotoxicity such as cell death in the human body during drug delivery. Both carboxyl and thiol groups contained in GSH can be combined with gold nanoparticles by chemical adsorption. Gold nanoparticles pretreated with GSH can inhibit cell death compared with gold nanoparticles alone, which provides a reliable idea for reducing the biotoxicity of gold nanoparticles [4]. In addition to being used as nanocarriers to enter lesions, gold nanoparticle-based sensors can also provide help for lung cancer screening, which can provide a faster and cheaper screening method.

In addition to gold, silver nanoparticles can also make a great contribution to the treatment of lung cancer nanomedicine. The smaller the particle diameter of silver nanoparticles, the better the penetration and targeting, the role of silver nanoparticles as carriers and antibacterial drugs can be effectively played, and the silver nanoparticles can be directly used as anticancer drugs as silent treatment materials. One characteristic of Ag-NPs is consistent with cancer cells, that is, with the rapid proliferation of cancer cells, cancer cells will accelerate their division and exhibit a greater metabolic rate, which leads to a more rapid internalization of Ag-NPs, leading to cell death. Studies have shown that silver nanoparticles can prevent and attenuate cancer by comparing vehicle-treated tumors with silver nanoparticles-treated tumors and have a good selectivity for non-small cell lung cancer, which is a good tool for early prevention and diagnosis of lung cancer [5].

3. Nanoscale metal oxides

Nanoscale metal oxides such as iron oxide can be used as nanomedicine carriers for lung cancer treatment. Iron oxide has good thermal stability. For targeted drug delivery, iron oxide nanoparticles have the advantages of low biotoxicity, large specific surface area, and strong penetration ability, which make them a good choice for nano-drug delivery. It has been shown that iron oxide nanoparticles are formed through the decomposition of diiron(III)-Schiff base precursor at high temperatures up to 700 degrees Celsius and the progressive cleavage of diiron under nitrogen environment. Iron oxide nanoparticles showed promising inhibitory activity against different types of pathogens by diffusion method. Nanoscale iron oxide has the structural advantage of entering the oxygen interactions within the cell, thereby causing oxidative stress.

The destruction of cell structure by nanomaterials is the key to the inhibition of cell growth, so as the concentration of iron oxide nanoparticles increases, the bactericidal effect will also be enhanced. Similar to human lung cancer cell lines, previous studies have shown that iron oxide nanoparticles have a significant effect on cancer cells. Compared with the untreated control group, the survival rate of cells treated with iron oxide nanoparticles was only half that of the control group. The growth of cells could also be understood by cell morphological observation. After AO/EB staining, the normal cells were green, the apoptotic cells were orange, and there would be cell membrane rupture, cell shrinkage and other phenomena. About half of the orange cells could be observed in the cells treated with iron oxide nanoparticles. About 45% of the cells died of apoptosis and about 6% of the cells died of necrosis. In addition, mitochondria are the key to providing energy and transmitting signals to the cell. Once mitochondria lose function in apoptosis, cytochrome C is released by mitochondria in the cell. Cationic dye JC-1 can detect the depolarised color change of the mitochondrial membrane. Ordinary cells will appear green, while mitochondrial membrane depolarised will cause the dye to appear orange. Cells induced by iron oxide nanoparticles will appear orange, indicating that iron oxide nanoparticles can

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cause the loss of mitochondrial function. The role of iron oxide nanoparticles as antibacterial agents has been well established, but the delivery of drugs to the A549 cell line needs more perfect studies.

The non-porous and mesoporous silica and the combination of non-porous and mesoporous silica coatings were attached to the superparamagnetic iron oxide nanoparticle (SPION). The feasibility of hyperthermia treatment with superparamagnetic iron oxide nanoparticles coated with silica is still maintained, and this coating can effectively inhibit the release of iron ions, which is more suitable for the diagnosis and treatment of nanoparticles, and also provides sufficient drug delivery opportunities in terms of structure, because SPION can bind to lung epithelial cells. Therefore, nanoparticles loaded with cancer drugs can be delivered directly into the lungs through breathing, and the combination with magnetic heating therapy will play a good role [6].

In addition to being used for drug delivery, iron oxide nanoparticles can also be used to construct SPION suitable for MRI immunoimaging by coating with oleic acid and carboxymethyl dextran and coupling with monoclonal antibodies in mice to form magnetic nanoparticles. These particles can improve the detection limit by in vitro MRI imaging, and the particles also can target A549 cells, which can play a role in targeted therapy and imaging [7]. SPION is a commonly used T2 contrast agent in clinical imaging. Existing techniques can apply SPION to the liver and gastrointestinal tract, but the high dispersity of SPION leads to a lack of specificity in imaging. To improve this method, a hydrophobic surfactant is attached to the surface of SPION. After applying surfactant, the tissue penetration can be enhanced, the original magnetic properties can be maintained, and the lung cancer cells can be targeted, which provides help for the molecular diagnosis of lung cancer [8].

Apart from iron oxide, which can be used as nanoparticles for the effects and treatment of lung cancer, tunable zinc oxide nanorods (ZnO NRs) can be used for anti-cancer applications due to their photocatalytic properties. The leaf extract of C. pschannae was used as a reducing agent to reduce zinc acetate, and zinc oxide nanorods were synthesized through this green method. The photocatalytic and antioxidant properties of ZnO NRs were determined by dose and reaction time. The activity of ZnO NRs was verified by lung cancer cells, and it was found that the anti-cancer mechanism of ZnO NRs was the same as that of iron oxide nanoparticles, i.e., ZnO NRs also induced cell apoptosis through oxidative stress. This green and eco-friendly nanoparticle may also have good potential in the future [9].

4. Non-metallic nanomaterials

Among the non-metals, carbon in various forms is the most used nanoscale modality for lung cancer treatment. Carbon nanodots (C-dots), for example, are nanoscale materials with special optical properties, high biocompatibility and chemical inertness, making them an excellent choice for biomedical applications. The characteristic optical properties of carbon nanodots, blue-shift photoluminescence, are determined by the particle size reduction. Due to the photoluminescence properties of carbon dots, they are well suited to be used as a contrast agent, to help in the diagnostic process, and to be treated by gene silencing therapy, which affects tumor genetics with specific siRNA and induces apoptosis through siRNA and corresponding mRNA. Experiments show that carbon nanodots mixed with carbon nanodots and siRNA can reduce the viability of H460 cells by about 30%, and the expression of cyclin can also be inhibited [10]. Targeting mitochondria in lung cancer cells is also an important part of the targeted drug therapy process.

The therapeutic modality of nanotube (CNT)-ABT737 (PEG-CNT-ABT737) nanodrugs is also worthy of attention. ABT737 is a potent anti-tumor drug targeting Bcl-2. PEG-CNT-ABT737 is suitable for transfer into endosomal cells after vesicular uptake, is stable in an environment mimicking blood pH, and can also be released by an enzymatic reaction. The mitochondrial signaling pathway is the key to the apoptosis of A549 cells. Therefore, with the increased uptake of PEG-CNT-ABT737, the release of cytochrome C and the inhibition of Bcl-2 eventually lead to the apoptosis of A549 cells [11]. In addition, carbon nanoparticles can also be used as good drug therapy for lung cancer. One of the emerging polysaccharides derived from CNT has a controllable size, functionalized surface, and photothermal properties under near-infrared light. It has not yet shown cytotoxicity in mouse macrophages, and it has also shown good compatibility in human plasma and blood. According to studies, the nanoparticles were

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stable and did not exhibit cytotoxicity in lung cancer cells (A549) and (NCI-H1650) when administered in large quantities without being activated by NIR. However, when activated by NIR light, CNTs exhibited their photothermal properties and phototoxicity. When compared with the control group without CNTs, which could be maintained under NIR light for 15 minutes, the viability of A549 cells was significantly decreased [12].

5. Conclusion

This paper reviews the application of inorganic materials such as metal NPs, nanoscale metal oxides and non-metallic nanomaterials as drugs and drug carriers in the treatment of lung cancer. Lung cancer accounts for 18.4% of all cancer deaths worldwide, and there is an urgent need for better treatment methods. As a more biologically advantageous way to treat lung cancer, nanoscale targeted therapy has been deeply studied. Metals, metal oxides and nonmetals are inorganic materials for nanoscale therapy. It has been known that biocompatibility, chemical inertness, indicating functionalization, aqueous dispersion, and optical properties are all factors to be considered in nano-targeted therapy. For example, the effect of gold nanoparticles on cells is not universal, and the effect on different cells and the mechanism of action still need to be explored. In terms of Ag NPs, their metabolic rate and internalization characteristics still need to be studied, and there is still a lack of theoretical basis for in vivo application. Inorganic materials can also be fused with organic materials to use each other's advantages to develop targeted drug therapy with higher adaptability and better application performance. More drug delivery principles, drug activation methods, and carrier materials need to be explored in the future.

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