Research on the Advances in the Application of Superparamagnetic Iron Oxide Nanoparticles in Targeted Diagnosis and Treatment in Pancreatic Cancer

Jiayi An

[1]*Beijing National Day School China, Beijing,100000, China*
**Corresponding author.Email: an18613316667@163.com*

ABSTRACT

Superparamagnetic iron oxide nanoparticles (SPIO) are medical nanomaterials with the advantages of super-magnetic, surface modification and targetedness. At the same time, superparamagnetic iron oxide nanoparticles are beneficial for magnetic resonance imaging, but also can be combined with photodynamic therapy, photothermal therapy and magnetic heat therapy to treat tumors in the human body. Pancreatic cancer can be treated with superparamagnetic iron oxide nanoparticles. Pancreatic cancer is the "king of cancer" in the field of oncology, one of the worst malignant tumors in prognosis. Superparamagnetic iron oxide nanoparticles can properly solve the problem of low diagnosis and cure rate of pancreatic cancer. In this paper, the performance characteristics of SPIO and the application progress of SPIO in the diagnosis and treatment of pancreatic cancer are reviewed. In this paper, superparamagnetic iron oxide nanoparticles are studied by literature reference. While referring to relevant papers, the author also thinks and conceives. The main research directions are the preparation of SPIO, the advantages of targeted SPIO, the application of SPIO in magnetic resonance imaging, the principle of targeted drugs, and the principle of magnetic heat therapy for pancreatic cancer. The main results are as follows:1.Superparamagnetic iron oxide nanoparticles have many advantages, such as magnetic sensitivity, easy surface modification, targeting and high relaxation properties. 2. The preparation methods of SPIO are various, but the chemical coprecipitation method is widely used because of its simple operation, low cost and low requirements for the laboratory environment. 3. Active targeting SPIO is more effective in the diagnosis of pancreatic cancer. It can be used in magnetic resonance imaging to improve the clarity of imaging. 4. SPIO can be used to treat pancreatic cancer through targeted drugs and magnetic heat therapy.

Keywords: *Superparamagnetic iron oxide nanoparticles; pancreatic cancer; magnetic heat therapy; magnetic resonance imaging (CT); Targeted drug carriers*

1. INTRODUCTION

With the development of science and technology, nanomaterials are more and more used in the medical field. Superparamagnetic iron oxide nanoparticles are important biomedical nanomaterials. In addition to NMR, they can also target drug loading and hyperthermia. At present, superparamagnetic iron oxide nanoparticles are common magnetic resonance contrast agents, which are easy to be chemically modified. If combined with specific ligands, they can form active targeted SPIO. Targeted SPIO is more accurate, which can realize clear magnetic resonance imaging, targeted drug delivery and local hyperthermia. SPIO has a high magnetocaloric effect. It can kill tumor cells through thermal conductivity and is used in hyperthermia. The side effects of hyperthermia are less than those of radiotherapy and chemotherapy. Many advantages of SPIO make it a popular contrast agent and diagnostic reagent in the clinic. However, the understanding of SPIO's metabolic pathway and toxicity to human body is not deep enough, which affects its further application. In the future, people will apply SPIO to more fields and disease treatment. Pancreatic cancer is cancer with hidden development, rapid progress and poor prognosis. It is known as the "king of cancer". The 5-year survival rate is only 8.4%, and the effect of surgery and

chemotherapy is not ideal. Therefore, early clinical diagnosis is particularly important, but the effective treatment methods and the mechanism of occurrence and development are not yet clear, and the mortality rate of pancreatic cancer remains high. Superparamagnetic iron oxide nanoparticles can be used to diagnose pancreatic cancer more accurately and improve the efficiency of treatment.

2. PREPARATION METHOD FOR SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES

The preparation methods of superparamagnetic iron oxide nanoparticles are divided into two aspects: physical methods and chemical methods. Compared with physical methods, chemical methods are more controllable, accurate and efficient. The common methods of chemical preparation of SPIO include a hydrothermal method, high-temperature pyrolysis method, microemulsion method, a coprecipitation method and so on.

2.1. Chemical Coprecipitation Method

The commonly used method is chemical coprecipitation. Compared with other methods, this method has the advantages of simpler operation, lower cost and low requirements for experimental conditions, so it is widely favored by everyone. The specific experimental methods are as follows: alkali is added to divalent iron chloride（$FeCl_2$）and trivalent iron chloride ($FeCl_3$) with a molar ratio of 2:1. The black product, Iron oxide, is obtained after reaction precipitation. The chemical reaction formula is as follows:$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O$. Iron oxide ($Fe_3O_4$) will become to the hollow magnetic nanoparticles by adding dextran solution, high-speed stirring, high-speed centrifugation and magnetic separation. The size of nanoparticles is related to the type and proportion of salts used in the experiment, pH value and ionic strength.

2.2. Microemulsion Method

Microemulsion method is the formation of oil in water (W/O) or oil in water (O/W) microemulsion under the influence of surfactants[1]. Two kinds of microemulsions, such as nucleation, coalescence and agglomeration, are finally obtained through heat treatment. The reaction is carried out inside the microemulsion droplet, which can effectively prevent particles from further agglomeration. Therefore, the particle size is uniform, and the size of the particles can be controlled by controlling the amount of surfactant. The (Fe_3O_4) nanoparticles are mostly spherical and dispersible, but this method uses more surfactants and has a higher production cost.

3. THE CHARACTERISTICS OF SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES

SPIO has different magnetic characteristics from bulk materials. Due to the reduction of magnetic materials, SPIO shows superparamagnetism, that is, SPIO shows high magnetism when the external magnetic field is applied; When the external magnetic field disappears, the magnetism of SPIO will also disappear. SPIO has the advantages of large specific surface area, high safety, high relaxation performance, easy surface modification, magnetic sensitivity and so on[2]. SPIO has good biocompatibility and low toxicity. SPIO are mainly metabolized by reticuloendothelial phagocytosis system after entering human body. The Lysozyme will rapidly dissociate SPIO and release iron ions. Macrophages will phagocytize ferritin receptors. Iron ions enter the normal iron metabolism process of human body through binding with ferritin[3]. Human body will excrete SPIO through feces and urine. The hydrophobic surface of unmodified SPIO will aggregate into micron groups due to hydrophobic effect, which reduces the surface area of SPIO, so the functionality of SPIO is reduced. However, the surface modification of SPIO can enhance the stability of SPIO suspension.

4. TARGETED SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES USED TO DIAGNOSE PANCREATIC CANCER

4.1. Targeted Superparamagnetic Iron Oxide Nanoparticles

Unmodified SPIO is encapsulated by biocompatible molecules and functional surface modification to become targeted SPIO. Targeting technology can be divided into passive targeting and active targeting. Magnetic nanoparticles use their small particle size to enter the human body barrier. Macrophages in the reticuloendothelial system actively phagocytize magnetic nanoparticles and make them aggregate in human organs with rich reticuloendothelial tissue to form passive targeting. Active targeting needs to be accomplished by modifying the surface or connecting specifically targeted ligands. Active targeting is more advantageous in the diagnosis of pancreatic cancer[4]. First of all, because the pancreas is not rich in reticuloendothelial tissue relative to the liver, it can not clearly reflect the gap of nanoparticle concentration, which is not easy to diagnose. Second, magnetic nanoparticles can enter specific sites more effectively with the help of targeted ligands, improve particle concentration and imaging degree, and reduce the damage of normal cells around cancer.

4.2. Diagnosis of Pancreatic Cancer with Superparamagnetic Iron Oxide Nanoparticles Magnetic Resonance Imaging (CT)

The use of SPIO as a contrast agent for MRI can solve the problems faced by commonly used contrast agents in imaging pancreatic cancer[5]. Gadolinium is a commonly used contrast agent for magnetic resonance imaging, which can reflect the blood supply of lesions and increase the accuracy of diagnosis. However, for early pancreatic cancer with poor blood supply, gadolinium can not be sensitive and accurate to point out the lesion, because gadolinium is non-specific in the human body, and has a certain degree of nephrotoxicity. But, SPIO can improve the resolution of magnetic resonance imaging by increasing the resolution of the MRI by combining the specific targeting ligands, and increasing the contrast of the images, showing the tiny lesions more clearly, making an early diagnosis for pancreatic cancer patients. Urokinase-type plasminogen activator receptor (uPAR) is more sensitive and specific than the commonly used tumor marker of pancreatic cancer, carbohydrate antigen 19-9 (CA 19-9). The expression of uPAR in pancreatic cancer tissues was exceptionally high, and was almost not expressed in normal pancreatic tissues and chronic pancreatitis tissues. Therefore, uPAR is a good diagnostic cell surface receptor for pancreatic cancer. uPAR specific binding ligand ATF can be linked to the surface of iron oxide nanoparticles (IONP) to achieve magnetic resonance imaging of pancreatic cancer. IONP formed by SPIO and u par specific binding ligand ATF can be used as a contrast agent to form magnetic resonance imaging[6]. Secondly, superparamagnetic iron oxide nanoparticles themselves can shorten the transverse relaxation (T2) time of body tissues during magnetic resonance scanning, increase the difference of magnetic resonance signals and increase the resolution of diseased tissues. In addition, integrins associated with many cancers can also enhance the targeting of pancreatic cancer cells by binding to peptides from the RGD three peptide sequence.

5. TARGETED DRUG TREATMENT FOR PANCREATIC CANCER

Superparamagnetic iron oxide nanoparticles have superparamagnetism, which is a necessary condition for them to become the targeted carrier of anticancer drugs. The superparamagnetism of SPIO has a linear relationship with the size of nanoparticles. When the size of nanoparticles is 10 ~ 20 nm, its magnetic strength increases under the action of the external magnetic field, superparamagnetic iron oxide nanoparticles carry drugs to target cells; After removing the magnetic field, the disappeared SPIO will not form a mass, which eliminates the possibility of thrombosis and blocking blood vessels, avoids being swallowed by macrophages in the body, and can stay in the blood circulation of the human body for a long time. Because nano SPIO has magnetic sensitivity, SPIO drug carrier has a higher tissue diffusion rate and lower sedimentation rate. SPIO with a diameter of 10 ~ 100 nm[7] can not only escape the phagocytosis of the reticuloendothelial system and maintain a longer time in the blood circulation, but also play a diffusion effect in the capillaries and make the drugs penetrate into the lesions. In addition, the surface coating of SPIO can better combine drugs with target cells, improve reaction efficiency and biocompatibility, and avoid the mutual aggregation and oxidation reaction of SPIO. The drug is combined with the surface coating material to form electrostatic action, hydrophilicity or hydrophobicity, so that SPIO can resist the surrounding environment during transportation and effectively deliver the drug to the designated area. At present, the typical representative material is a magnetic liposome, which has good retention efficiency and can maintain stability. Magnetic liposomes can carry more drugs to achieve the best magnetic reaction and maximum drug efficiency. The magnetic liposome can also combine hydrophilic drugs and lipophilic drugs at the same time, so as to diversify the types of drugs that can be combined. However, the surface coating will weaken the magnetism and reduce the targeting of SPIO as drug carriers. The targeted transport of drugs mainly depends on the external magnetic field and the size of SPIO. The principle of passive targeted transport is that the size of SPIO can reach the required position. The gold standard of antitumor drugs is the penetration effect and retention effect. Adjusting the intensity of the external magnetic field can help the drug reach the target and then be released.

6. DISCUSSION

At present, the basic treatment principle of pancreatic cancer is surgical treatment, followed by radiotherapy and chemotherapy. In recent years, due to the improvement of technology, magnetocaloric therapy has emerged[8]. Tumor magnetocaloric therapy is safe, effective and hasfew adverse reactions. It has been used in the clinical treatment of glioma and prostate cancer. Superparamagnetic iron oxide nanoparticles can produce heat energy under the action of alternating magnetic field, which is transmitted to tumor cells through magnetic nanoparticles. Because the heat resistance of normal cells and tumor cells to temperature is inconsistent, local heating will only kill tumor cells and cause less damage to normal cells around the tumor. The active targeting formed by the combination of SPIO and uPAR specific binding ligand ATF can accurately deliver the magnetic materials for hyperthermia introduced intravenously or directly to the diseased tissue to complete targeted hyperthermia[9]. RGD Peptides targeting $\alpha_v\beta_3$ receptors can also be

connected to SPIO to construct SPIO with active targeting for magnetic hyperthermia.

At present, magnetocaloric therapy is not applied in the clinical treatment of pancreatic cancer.

Pancreatic cancer is a highly malignant tumor with poor prognosis and low cure rate. Early diagnosis and early treatment are the key to improve and improve the prognosis of pancreatic cancer. The integration of tumor diagnosis and treatment through nanoparticles has been a research hotspot in recent years. Superparamagnetic iron oxide nanoparticles can simultaneously improve the diagnosis rate and therapeutic effect of pancreatic cancer. SPIO is a good research object. At present, people have developed specific diagnosis and treatment methods related to SPIO by using its characteristics. However, some methods can be used in clinical treatment only after further verification by researchers. In the future, people should deeply study the biosafety of SPIO and the toxicity of surface modifiers and coatings after degradation, and expand the use of nanomagnetic materials for the diagnosis and treatment of pancreatic cancer, as far as possible to improve the early diagnosis and cure rate of pancreatic cancer.

7. CONCLUSION

In conclusion, the clinical symptoms of pancreatic cancer are obscure, with high malignancy and poor prognosis. The method of combining superparamagnetic iron oxide nanoparticles with molecular imaging has been developed to improve the early diagnosis and treatment of pancreatic cancer. Superparamagnetic iron oxide nanoparticles have the characteristics of targeting, easy surface modification and low toxicity. SPIO can be widely used in magnetic resonance imaging and targeted drug delivery because of its good characteristics. If combined with specific tumor markers, active targeted imaging and therapy with higher accuracy can also be formed. At present, researchers have some research results in the diagnosis and treatment of pancreatic cancer by SPIO. However, there are many magnetic nanoparticles corresponding to tumor treatment methods that have not been applied in the clinical treatment of pancreatic cancer. In the future, SPIO will play a new role in the early diagnosis and treatment of pancreatic cancer. At the same time, it will also deeply study the security and effectiveness of superparamagnetic iron oxide nanoparticles, which have a broader application prospect.

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