Study On Synergistic Mechanism of Multimodal Combination in Tumor Optical Therapy

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Abstract. With the development of the times, environmental pollution and bad living habits have gradually increased the incidence of cancer in human beings, and the global cancer mortality rate has surged. The treatment of tumor has become a major concern of human beings. Tumor growth and spread are highly heterogeneous, so integrated treatment of cancer has become a new trend. This paper explores the mechanism of multimodal combinations to generate synergistic effects in optical tumor therapy involving combinations of nanocarrier system, chemotherapy, nano platform, photosensitizer, catalyst, immunomodulator and photothermal agent. The results of this paper indicate that combination therapy can break the limitations of single therapy and traditional therapy and realize the synergistic mechanism in treatment. In the face of many difficulties and challenges, combined therapy has great potential and development prospects. It is expected that the optimization and selection of the research program and the clinical application of the combination therapy can get a major breakthrough.

Keywords: Tumor; Combination Therapy; Synergistic; Photothermal Therapy.

1. Introduction

There are two types of tumors, benign and malignant. Benign tumor cells grow slowly, do not spread, and are generally treatable. Malignant tumor cells grow fast and spread easily and can easily cause death. The traditional treatment of tumor includes surgery, radiotherapy, chemotherapy and so on. Although the surgery can directly remove the tumor, but for the tumor that has begun to spread, the surgical treatment will not be able to cure it, and the tumor will still recur. Radiation can be directly injected into the tumor, killing tumor cells and controlling the spread of tumor cells, but damaging the surrounding normal tissue. Chemotherapy uses chemotherapeutic drugs to kill or suppress tumor cells, but can have a range of side effects such as diarrhea, nausea, vomiting, and drug resistance. Optical therapy is widely used in the field of cancer, and it is an excellent alternative or complementary means compared with traditional methods [1]. Photodynamic therapy has a wide range of applications and does not harm surround normal tissue. Photothermal treatment has little side effect, short time and great effect. However, in the clinical application of optical therapy, how to use incident light to penetrate biological tissues to reach different depths of tumors to kill tumors is still a difficulty [2]. Based on these problems, the current research trends are combination therapy strategies and the preparation and improvement of novel nanomaterials. In recent years, researchers have focused more on the study of malignant tumors. In terms of treatment, it focuses on immunotherapy and drug delivery. This review aims to break down a single limitation of cancer treatment. Nanocarrier systems are used for photothermal therapy combined with chemotherapy, nano platform targeting and drug delivery assistance, photothermal agent combined with photosensitizer, catalytic therapy and immunotherapy, which are supported by specific case studies. Examples include Se-PEG-Au-Se NPs-DOX nanocarrier system, gold-cerium bimetallic asteroid nanoplatform, iron death combined with chemotherapy nanoplatform, gold nanoparticles, Prussian blue nanoparticles, high-entropy oxide composite carbon nanoparticles, and nano-vaccines [3-5]. Nanoparticles are widely used in the field of cancer because of their properties, generally between 1 and 100 nanometers. Nanoparticles are not only suitable for the diagnosis of tumors, but also for the treatment of tumors. Nanoparticles are targeted. By designing specific ligands, nanoparticles can be identified, targeted

and bound to tumor cells to deliver drugs. Nanoparticles can absorb specific wavelengths of light or magnetic field energy, creating a plasmon resonance effect that converts light energy into heat to kill tumor cells. Because of its fluorescence, paramagnetism, radioactivity and other characteristics, nanoparticles can improve the imaging resolution of CT, MRI and other imaging, and assist in the discovery of tumors. The nanoparticles can also link to specific antibodies that trap cancer cells to help diagnose tumors. In this paper, we will analyze the pathway of action and synergistic mechanism of various combination therapies, as well as the characteristics of various materials and drugs used in treatment.

2. Multiple-mode Combination Therapy for Tumor

Optical therapy can be divided into photodynamic therapy and photothermal therapy. Photodynamic therapy, which is non-invasive, rapid, highly sensitive and widely used, is to stimulate the photosensitizer by irradiation of a specific wavelength of laser to make singlet oxygen generation. Singlet oxygen can kill tumor cells and avoid spreading to normal cells. Oxygen is essential for photodynamic therapy, but the tumor microenvironment is characterized by a lack of oxygen. Photothermal therapy works by injecting a photothermal conversion material into the tumor site and targeting tumor cells under near-infrared light. The photothermal conversion material is irradiated to convert light energy into heat energy, raising the local temperature to kill the tumor cells. However, due to the limited depth of light penetration, only subcutaneous tumor therapy can be performed. Faced with a series of problems in photothermal therapy, the development of multi-mode combined anti-tumor is an effective way to solve the limitations. Photothermal agents can be combined with catalysts, photosensitizers, chemotherapeutic drugs, immunomodulators, etc [6]. The combination of photothermal therapy, radiotherapy, chemodynamic therapy and chemotherapy can also be combined with the nano platform. Combination therapy can overcome the limitations of monotherapy and achieve a synergistic anti-tumor mechanism.

2.1. Nanocarrier System, Photothermal Therapy and Chemotherapy

Se-PEG-Au-Se NPs-DOX (SePAD) is a bi-functional nanoparticle carrier system that can treat breast cancer based on dynamic Au-Se interaction triggered by 808nmNIR laser [3]. This novel controlled release nanocarrier system is used for photothermal therapy combined with chemotherapy to realize chemical-photothermal synergistic tumor therapy [3]. The system structure is stable in an environment rich in glutathione (GSH). GSH has the ability to maintain the stability of the immune system and can also be used as a therapeutic drug. In the SePAD system, antitumor drug doxorubicin was injected into gold nanoparticles (Au NPs) containing diselenide copolymer (mPEG-Se-PEGm) and AU-Se bond interaction [3]. SePAD has highly efficient photothermal properties, maintaining environmental stability and controllable behavior of delaying the release of reconstructive stimulus Dox [3].

Au NPs in SePAD system is a kind of nanomaterials with wide application. Therapeutic drugs can bind to sulfur atoms, which bind to the surface of Au NPs. As a drug carrier, Au NPs can target the target location and deliver the drug to the cell. Au NPs can bind antibodies to tumor cells. Under specific laser irradiation, Au NPs produces a plasmon resonance effect that converts light energy into heat to kill tumor cells. Au NPs also has the advantages of biocompatibility, inertness, and high specific surface area. Therefore, SePAD chose Au NPs as the carrier to bind the drug to tumor cells. Au NPs, mPEG-Se-Se-PEGm and Dox Because mPEG-Se-Se-PEGm and Dox can be dissolved in water, they interact and connect in Au NPs aqueous solution [3]. Gold selenol (Au-Se) nanoplatforms have been reported to be replaced by Au-Se bonds due to the instability of Au-S bonds in high biothiol environments [7]. The Au-Se nanoplatform is extremely stable when transporting drugs in the body.

SePAD has high stability and Dox release efficiency in tumor environment with high glutathione concentration. SePAD under the irradiation of 2w/cm2NIR laser, SePAD under the irradiation of 10mM GSH and SePAD under the presence of 10nM GSH under the irradiation of 2w/cm2NIR laser

were compared. It is concluded that Dox release in the presence of 10nM GSH under 2w/cm2NIR laser irradiation during the same time is the highest [3]. It can be concluded that the nanocarriers can avoid the advance leakage of drugs before reaching the target position, and the efficiency of drug release is high. It was also concluded that the SEPad-containing group irradiated by NIR laser during the same time had obvious fluorescence signals, indicating that the SePAD self-assembled nanomaterial carrier had good stability in the GSH tumor environment [3]. It is realized that SePAD can control the photothermal release of Dox under the irradiation of NIR laser.

2.2. Nanoplatform

The Gold-cerium bimetallic asteroid nanoplatform (CeO2@GNSs/Myr-HA) is prepared by electrostatic adsorption of ultra-small cerium dioxide to nanostars, then loaded with myricetin and hyaluronic acid [4]. The nanoplatform contains three enzymatic properties that interact to kill tumor cells. The three enzymatic properties of glucose oxidase (GOD), glutathione oxidase (GSH-Ox) and peroxidase (POD) can interact to catalyze activity [4]. Myricetin is a polyhydroxy flavonol compound. As a chemical agent, it can be anti-inflammatory, anti-tumor, reduce neurotoxicity, enhance immunity and so on. Myricetin can inhibit the expression of vascular endothelial growth factor and inhibit angiogenesis of tumor cells through p38/MAPK signaling pathway [4]. Hyaluronic acid is an acidic mucopolysaccharide. It targets the CD44 receptor on the surface of tumor cells, which in turn is regarded as a receptor for hyaluronic acid [4]. Targeting of hyaluronic acid can release CeO2@GNSs/Myr-HA in the cytoplasm [4]. Nano-enzymes are simulated enzymes with both catalytic and nano-properties. Nanase has the advantages of high catalytic efficiency, biocompatibility, stability and low cost, and has been widely used in medicine, environment, chemical industry and other fields. For example, Cu-Prlm nanomases can produce more biologically toxic free radicals by catalyzing hydrogen peroxide in tumor cells. To achieve the role of catalytic anti-tumor.

Gold nanostars have the advantages of stability, high specific surface area and dispersion, and are selected for targeted drug delivery and controlled drug release. CeO2@GNSs/Myr-HA is a nanoplatform that combines enzyme catalysis, chemotherapy, and photothermal therapy [4]. It accumulates at the tumor site, binds to the CD44 receptor on the surface of tumor cells targeted by hyaluronic acid and phagocytes [4]. This then causes myricetin to be released into the tumor microenvironment for drug chemotherapy [4].

The nanoplatform for the combination of iron death and chemotherapy is cisplatin (Pt (II)) as a chemotherapy drug, and polybaolin (BAI) as an inducer of iron decline carboxymethyl chitosan (CMCS) as a drug carrier [5]. Pt (II) is a platinum-containing substance that binds to DNA, causing cross connections. Anticancer drugs that destroy the function of DNA and inhibit cell mitosis can be used in clinical treatment of thyroid cancer, lung cancer, malignant lymphoma, esophageal cancer, nasopharyngeal cancer and other tumors [8,9]. However, the use of Pt (II) has been restricted due to side effects, including strong toxicity to the kidney, possible peripheral neuropathy and reduced blood cell production [10-12]. In order to reduce the impact of side effects, the discovery of targeted drug delivery has greatly reduced the negative effects. Nanomedicine systems can deliver drugs to target locations and improve anti-tumor effects [13,14]. It can also increase the solubility of drugs by enhancing penetration and retention effects, prolong blood circulation and accumulate drugs in tumor tissues. To minimize toxicity [15].

CMCS has the function of promoting wound healing, antibacterial and moisturizing. It also has good water solubility, biocompatibility, renewable and easy to degrade. Carboxymethyl chitosan nanoparticles, suitable for drug delivery.

The nanoplatform uses CMCS as a carrier and connects Pt (IV) -COOH to CMCS [5]. Amphiphilic polymer prodrug (CMCS-Pt) was prepared [5]. BAI inhibits the mechanism of action of GPX4 and increases reactive oxygen species in tumor microenvironment, and Pt (II) promotes iron ion accumulation [5]. This nano platform combined with iron death and chemotherapy successfully and effectively inhibited the proliferation of tumor cells in vitro, providing a new idea for tumor treatment and a new strategy for cancer treatment.

2.3. Photothermal Agent and Photosensitizer

Oxygen in the tumor microenvironment is required to be consumed in the process of photodynamic therapy, but the hypoxic characteristics of the tumor microenvironment hinder the generation of single-line oxygen in the process of therapy, resulting in a vicious cycle. However, the photothermal treatment process is not limited by oxygen, and the combination of PDT and PTT can make up for the defects in the photodynamic treatment process [6]. PDT and PTT were combined for tumor synergistic treatment to enhance the therapeutic effect [6]. By combining photosensitizer and photothermal agent, a variety of nanomaterials have been used for combined tumor therapy. For example, Prussian blue nanoparticles are approved for clinical treatment by the US FDA because of their low toxicity, good catalytic performance, safety, high light stability, good biocompatibility and other characteristics. There is also the inorganic material Au NPs, which can be loaded with Prussian blue to form a core-shell Au@PB nanomaterials [16]. Because of its high photothermal efficiency, stability and high light absorption rate, it has good anti-tumor effect. However, the toxic side effects and biosafety of inorganic nanomaterials are difficult to be guaranteed, and the low bearing rate of organic nanomaterials is some defects. In the face of these defects, carrier-free nanomedicine in tumor therapy has been developed. It is a non-carrier self-delivery nanomedical based on the self-assembly of active drugs, with the advantages of up to 100% drug loading, non-toxicity, no damage to the immune system, simple preparation and so on [17].

The combination of photothermic agents and chemotherapeutic drugs can avoid the problems of organ toxicity, cell damage, reproductive toxicity and drug resistance caused by chemotherapy in tumor treatment. Nanomaterials can be loaded with chemicals to target areas, delivering drugs into cells. At the same time, photothermal treatment can increase the benefit and increase the local temperature. To achieve the purpose of improving the permeability of cell membrane and the cytotoxicity of drugs, the anti-tumor effect can be doubled with half the effort [18].

2.4. Photothermal Agent and Catalyst

Nanocatalytic therapy is a new approach to tumor therapy in the combination of photothermy and catalyst therapy. It is a kind of nanometer catalytic therapy based on the regulation of active oxygen species by combining photothermic agent and catalyst. It means that life must contain oxygen. This allows us to take advantage of factors such as hypoxia and glutathione enrichment in the tumor microenvironment. By regulating the oxygen content in the tumor microenvironment to control the tumor, nanocatalytic therapy can solve the two difficulties in the process of immunotherapy, the suppression of the immune microenvironment and the poor invasion of immune cells to the tumor.

High entropy oxide is a kind of polyoxide that solves five or more metal or non-metal oxides into each other. It has the advantages of structural stability, thermodynamic stability, photothermal performance, electrocatalytic performance and biocompatibility. It can not only be used as a photosensitizer in tumor therapy, but also in the field of photothermal catalysis. The synthesis of high-entropy oxide composite carbon nanoparticles (HEO/ CNPs) promotes the enhancement of enzyme-like activity with high NIR in catalytic therapeutic applications [19]. Under NIR laser irradiation, HEO/ CNPs exhibited highly efficient peroxidase and catalase activities [19]. The successful design and preparation of the hollow structure of high entropy oxide composite carbon nanoparticles makes it have a higher specific surface area and increase the active site. HEO/ CNPs has excellent POD/CAT-like enzymatic properties, which promote the conversion of endogenous hydrogen peroxide into highly active hydroxyl radicals [19]. It can alleviate the low oxygen content in the tumor microenvironment and kill tumor cells [19].

2.5. Photothermal Agent and Immunomodulator

The basis of tumor immunotherapy refers to the use of the tumor-immune cycle when the body's immune function is hyperactive or low. It restores the body to a normal state to control and eliminate tumors. Nano-immunotherapy includes cancer vaccine, monoclonal antibody type immune checkpoint inhibitor, cell therapy and so on. The tumor immune cycle is divided into seven stages:

tumor antigen release, tumor antigen presentation, activation and activation of effector T cells, T cell transfer to tumor tissue, tumor tissue T cell infiltration, T cell recognition of tumor cells, and finally the purpose of identifying tumor cells. Failure at any stage will lead to the escape of the tumor cells and the inability to clear the tumor cells. A bidirectional immunomodulatory nanovaccine based on tumor cell membrane was found in monotumor mice. It can be coated with immune adjuvant CpG oligodeoxynucleotide, black phosphorus nanoplates modified with Au NPs and indoleamine 2, 3-dioxygenase (IDO) inhibitor (NLG919) through tumor cell membrane to achieve tumor growth inhibition and establish long-term and effective immune memory in the body [20]. Nano-vaccines can improve the polarization efficiency of macrophages and reduce the expression of indoleamine 2, 3-dioxygenase [20]. The nanovaccine could be used in synergistic immunotherapy.

3. Conclusion

In summary, all kinds of combination therapy have synergistic anti-tumor mechanism. In general, the continuous exploration of combined therapy is an important direction of modern cancer treatment. Each treatment has its unique treatment mechanism, and a variety of combined treatments can play a different role. From different angles to kill tumor cells, the study of combination therapy overcomes the shortcomings of single therapy. By comparing different types of tumors, combined treatment schemes can be designed according to the types and specific conditions of tumors to improve the therapeutic effect of tumors and have a synergistic mechanism. A variety of treatments can interact with each other to complement the shortcomings and reduce the occurrence of adverse reactions. However, the current combination therapy of tumor is not mature enough and has drawbacks. Different patients due to their own physical and tumor conditions, so the treatment effect is uncertain, cannot guarantee the effect of treatment on patients. For patients with poor health and advanced cancer, the effect of combination therapy is not obvious and even leads to the deterioration of the patient's condition. Different tumors require different treatment regimens, and its complexity makes it difficult and expensive to develop. Both radiotherapy and chemotherapy have toxic side effects, and the side effects of combined treatment may increase. It is expected that the conundrum of combination therapy will be solved soon after exploration. Combined therapy can be successful in clinical application, so that the treatment of cancer can be a major breakthrough. A series of breakthroughs, such as the research and development of nano-vaccines, the preparation of new nanomaterials, the new discovery of nano-carrier systems, and the new exploration of nano-platforms, have made human beings take a big step forward in the field of tumor treatment. Combination therapy can reduce the global cancer death rate and improve the cure rate of cancer treatment.

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