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The Application of Modified Targeted Nanoparticles in Tumor Diagnosis and Treatment

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Abstract:

Nanoparticles (NPs) have been widely used in the field of oncology due to their characteristics such as non-invasiveness and targeting. Tumors are one of the major public health problems worldwide, and timely targeted diagnosis and treatment of tumors are particularly important. However, common nanoparticles have disadvantages such as insufficient targeting and poor adaptability to the tumor microenvironment (TME). TME can interact with tumors and jointly promote the tumor process. Moreover, at present, the single use of tumor diagnosis and treatment methods such as imaging techniques, surgery, photodynamic therapy (PDT) etc., may cause certain damage to the body, cannot conduct real-time monitoring, and lack targeting and other limitations. After being modified with specific materials, NPs can specifically target the TME based on the combined modifiers and can also integrate multiple modifiers to enhance the targeted positioning. The combination of the active targeting and non-invasive characteristics of NPs reduces the damage to normal tissues of the body. The combined application of nanotechnology with other diagnostic and therapeutic technologies can achieve real-time imaging detection at specific locations while conducting treatment, even achieve integrated diagnosis and treatment. This review explores the targeted effect of modified NPs on tumors and the application of NPs in combination with other diagnostic and therapeutic techniques.

Keywords:-Tumor microenvironment (TME); Modified nanoparticles; Targeted positioning; Diagnosis and treatment techniques

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I. Introduction

Tumors have a high incidence and mortality rate and are difficult to cure, remaining a major killer threatening life and health [1]. Timely detection of tumors is the key to treatment. The sole use of common tumor diagnosis and treatment methods, including imaging techniques, endoscopy, pathological diagnosis, surgery, PDT, etc., may have invasive characteristics, causing certain damage to the body, unable to conduct real-time monitoring, lacking targeting and selectivity, and causing adverse reactions [2] and other limitations. Using individual treatment methods one by one is rather time-consuming and labor-intensive.

The tumor microenvironment (TME) refers to the surrounding environment of tumor cells, which plays a vital role in processes such as the occurrence, development, invasion and metastasis of tumors [3]. Nanoparticles (NPs) refer to tiny particles with a size ranging from 1 to 1000 nanometers. Due to their non-invasive and targeted properties, they have broad application prospects in the field of tumor diagnosis and treatment [4]. However, common nanoparticles have limitations like poor targeting and easy removal and so on.

Modified nanoparticles are a technique that alters the properties and functions of nanoparticles by attaching specific modifiers to their surfaces. Modified nanoparticles can effectively solve the above problems. By attaching targeted modifiers like antibodies, peptides, and aptamers to the nano-surface, they can specifically combine with substances such as immune cells and tumor cells in the TME, overcome the passive targeting of nanoparticles that relies on blood vessels in tumor tissues of high permeability and retention effect, achieve active targeting of tumors, and significantly improve the targeting performance. It can also integrate multiple modifications to act on multiple targeted sites, enhancing the inhibitory effect on tumors. For instance, the semiconducting polymer nanocomposites (SPFeNOC) fabricated by Zhang, et al. is camouflaged by hybrid membranes. Through the design of the homologous targeting mechanism, nanoparticles can precisely target metastatic tumor cells and osteoclasts in bone metastatic lesions, thereby significantly improving the enrichment efficiency of nanoparticles at the tumor site.[5]; When nanoparticles are combined with other diagnostic and therapeutic methods, the targeted nature of nanotechnology is utilized to locate the tumor site, enabling the diagnostic and therapeutic techniques to be specifically carried out at the tumor occurrence site and reducing damage to other healthy tissues of the body. For example, when combined with imaging technology, real-time detection can be achieved, and it can be combined with treatment techniques like photothermal therapy (PTT), enabling diagnosis and treatment at the location of tumor occurrence. At the same time, combined with diagnosis and treatment technologies, it can endow nanoparticles with integrated diagnosis and treatment functions [5].

This review will introduce different types of modified nanoparticles and the combined application of nanotechnology with other diagnostic and therapeutic methods. Finally, it proposes that modified nanoparticles have great potential in the treatment of tumors and provide ideas for achieving the integration of diagnosis and treatment of tumors.

II. The application of modified nanoparticles

A. Single-Target Localization of Modified Nanoparticles

1) Single-target Localization of Nanoparticles Made of Polyethylene Glycol (PEG) Materials

Marina Talelli et al. modified EGa1 nanobodies onto the surface of doxorubicin-loaded core-crosslinked polymeric micelles DOX-PM micelles, enabling the micelles to actively target EGFR on the surface of tumor cells. Both in vivo and in vitro experiments demonstrated that the modified micelles enhanced the cellular uptake efficiency. Through this method, the enrichment of nano-micelles at the tumor site was effectively improved, enhancing the therapeutic effect [6]. Dong, et al. invented a new type of reactive oxygen species (ROS) oxidizing reactive polyethylene glycol - paclitaxel prodrug (PEG-B-PTX) [7]. Insert a benzylboronic ester linker between PEG and paclitaxel (PTX). The chemical properties of benzylboronic ester linkers are stable under normal physiological conditions. However, the presence of high concentrations of ROS in tumor tissues can oxidize the benzylboronic ester linker and self-lyse the linker, thereby releasing PTX and achieving precise drug release at the tumor site (Figure 1).

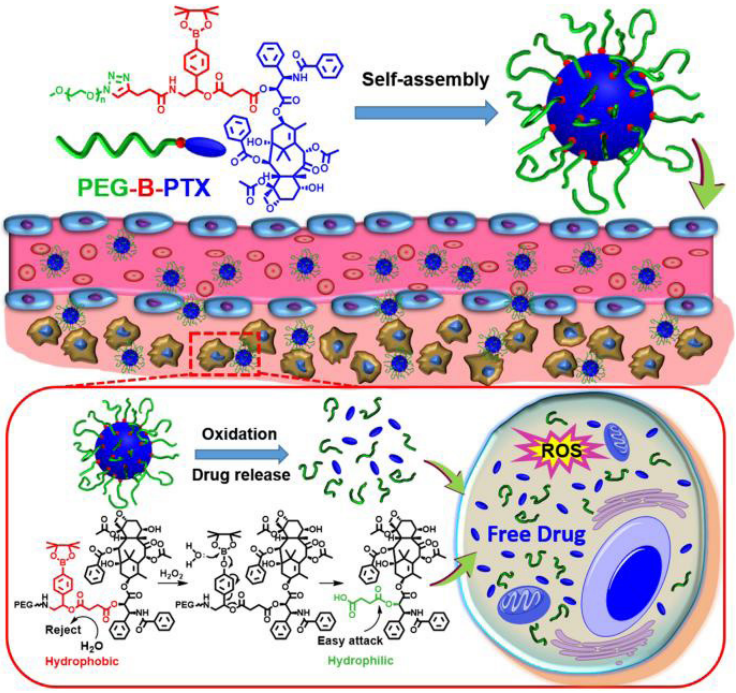

Figure 1. PEG-B-PTX before the chemical structure and the self-assembly into drug micelles, used in tumor ROS triggered drug release [7]

1)

2) Single-Target Localization of Nanoparticles in Gold Nanoparticles (Aunps) Materials

Diethylstilbestrol (DES) is widely used in livestock feeding, but excessive DES has teratogenic [8], mutagenic [9] and carcinogenic [10] characteristics. Wang, et al proposed an ultrasensitive method based on double-codified AuNPs (DC-AuNPs) of time resolved fluoroimmunoassay (TRFIA) for determination of DES. AuNPs modified with anti-DES antibody and SH-dsDNA-biotin were used to form DC-AuNPs. The fluorescent marker Eu(III) was introduced by SH-dsDNA-biotin through the Biotin-Streptavidin system. After adding the enhancement solution, Eu(III) dissociates from the complex and forms a strong fluorescence chelate. Background interference is eliminated through time resolved detection to achieve signal amplification. DC-AuNPs provides a new method with high specificity and stability for the ultrasensitive detection of DES through targeted immune recognition and signal amplification strategies [11,12].

3) Single-Target Localization of Nanoparticles in Liposome (Lip) Materials

To prevent tumor proliferation and metastasis, Li, et al. synthesized phosphatidyl choline reversed choline phosphate lipid (CP-Lip), modified it with PD-L1 antibody (CP-αPDL), and loaded with doxorubicin hydrochloride (Dox) to construct nanomedicines (Dox@tCP-Lipos). In the melanoma-model mouse (B16-F10 cells) experiment, the αPDL on the nanoparticles targeted and bound to the PD-L1 protein on the B16 cells, enriched in the tumor area and exerted its effect.

In summary, nanoparticles of different materials all utilize various surface-added modifiers to enhance the targeting effect of nanoparticles on individual substances or individual carcinogens in the TME through oxidation reactions, receptor-ligand binding, immune responses, etc., thereby improving the targeting efficiency.

B. Dual-Targeted Localization of Modified Nanoparticles

1) Dual-Targeted Localization of Nanoparticles Made of Polylactic Acid-Glycolic Acid Copolymer (PLGA) Materials

PLGA is a biodegradable polymer material produced by the polymerization reaction of lactic acid and glycolic acid. The biomimetic nanoparticles HPA/AS/CQ@Man-EM developed by Peng, et al. Mannose-modified erythrocyte membrane (Man-EM) was applied to the surface of HPA/AS/CQ nanoparticles, in which the ligand mannose specifically binds to the mannose receptors on tumor cells and M2-like tumor-associated macrophages (TAMs). To achieve dual targeting. Tumor growth was significantly inhibited in Colorectal cancer (CRC) mouse treated with HPA/AS/CQ@Man-EM. The expressions of Ki67 and VEGF in the tumor tissues of CRC mouse decreased, the infiltration of CD4 T cells increased, and the repolarization effect from M2 to M1-like TAMs was significant. All

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these fully demonstrate the important role of mannose modification in improving the targeted therapeutic effect of nanoparticles [13].

2) Dual-targeted Localization of Nanoparticles Based on Chitosan (CS) Materials

Niu, et al. constructed a ternary supramolecular assembly (FACA/TPPS ⊂ MPCD) using morpholine-modified permethyl β-cyclodextrin (MPCD), sulfonated porphyrin (TPPS), and folic acid-modified chitosan via multivalent interactions (FACA), and the finished product had a dual-targeting effect on lysosomes and cancer cells [14]. Firstly, MPCD and TPPS form a binary complex through complexation. Porphyrin core of fluorescence emission intensity by inhibiting π-stacking to strengthen, at the same time make the binary complex can be targeted action in lysosome. Further assembly with FACA forms FACA/TPPS ⊂ MPCD. Flow cytometry shows that folic acid targeting significantly enhances the uptake of nanoparticles by cancer cells. In the lysosomes of cancer cells, FACA/TPPS ⊂ MPCD accumulates highly and effectively generates reactive ROS, thereby inducing more significant cell death upon light exposure. The ternary system provides a new, efficient and low-toxicity strategy for the precise imaging and treatment of tumors through the synergistic effect of multiple components (Figure 2).

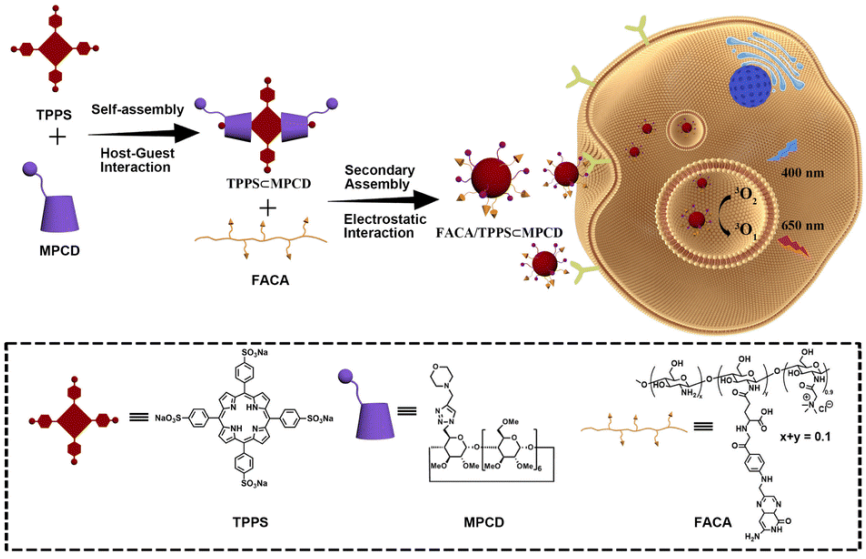

Figure 2. Schematic diagram of ternary dual-targeted supramolecular assembly FACA/TPPS ⊂ MPCD [14].

1)

3) Dual-Targeted Localization of Nanoparticles in Liposome (Lip) Materials

A large number of blood vessels can provide nutrients for the growth and metastasis of tumors [15]. As an important regulatory link of angiogenesis, the activation and proliferation of vascular endothelial cells play a significant role in promoting the germination and extension of new blood vessels. Wang, et al. developed for the first time A novel dual-ligand modified liposome (CUCA/GA&Gal-Lip) co-loaded with curcumin (CUR) and Combretastatin a-4 phosphate (CA4P) for anti-liver cancer treatment to block angiogenesis and inhibit tumor development [16]. Nanoparticles are modified by glycyrrhetinic acid (GA) and galactose (Gal), which can specifically bind to the protein kinase Cα and asialoglycoprotein-receptor respectively to improve the targeted delivery of liver tumors. The CUR and CA4P contained therein can significantly inhibit tumor angiogenesis by blocking the vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway.

The nanoparticles of the above three materials, through the addition of modifications, enable the nanoparticles to target and act on the dual targets in the TME. Compared with targeting a single target, dual targets also increase the aggregation of nanoparticles at the tumor site.

III. The combined application of modified nanoparticles and diagnostic and therapeutic technologies

A. The Synergistic Effect of the Combined Application of Nanotechnology and Other Diagnostic and Therapeutic Technologies

Magnetic hyperthermia (MHT) is an induction heating hyperthermia composed of magnetic nanoparticles (MNP) and alternating magnetic field (AMF). Tetsuya Kaga-

wa et al. developed anti-HER2 antibody-linked SPION nanoparticles (anti-HER2 SPION), which specifically entered HER2-positive AU565 cells only. The combined application of AMF and anti-HER2 SPIONs. In vitro experiments, cancer cells with HER2 overexpression (such as AU565 cells) were inoculated into culture dishes, and targeted localization was first carried out using anti-HER2 SPIONs. anti-HER2 SPIONs can fully bind to cells and be taken up by cells. After that, a 2.4kW radiofrequency generator is used to generate AMF. Place the culture dish on the coil which generates AMF, and apply AMF for magnetic hyperthermia with an amplitude (H) of 31 kA/m and a frequency (f) of 280 kHz. Experiments have proved that anti-HER2 SPIONs or AMF alone have no significant effect on cell viability. However, when the two are combined, they can significantly increase the death of HER2-expressing cancer cells (such as AU565 cells) [17].
Addressing PDT is limited by photosensitizers (PS) lacking tumor selectivity and hypoxic TME. The M/L-EApt developed by Zhen et al. is an integration of liposomes modified by anti-epidermal growth factor receptor (EGFR) -aptamer (EApt) and tumor cell membranes (TM). PHI@M/L-EApt is further formed from M/L-EApt loaded with oxygen carriers perfluorotributylamine (PFTBA) and IR780 (aPS). The engineered nanosystem with increased PFTBA and IR780 accumulation of PHI@M/L-EApt in the tumor can reverse hypoxic TME and enhance ROS production, paving the way for the efficacy of PDT in tumor treatment [18].
Immune checkpoint inhibitors play a very good role in anti-cancer. However, the current situation of their low objective response rate in clinical application remains a key bottleneck problem restricting the wide promotion and therapeutic effect improvement of this type of therapy. Riki Cho et al. explored the combined application strategy of anti-programmed cell death 1 (aPD-1) monoclonal antibodies (mAbs) and VEGFR2 gene knockdown technology in tumor endothelial cells. This strategy innovatively integrates immune checkpoint inhibitors with nanotechnology and can well overcome the above problems. The RGD-modified lipid nanoparticles (LNP) composed of ssPalmO-Phe can be used to deliver siRNA to TEC within xenograft tumors. Modified by RGD, LNP can selectively deliver siRNA to endothelial cells to induce knockdown of Vegfr2, thereby promoting the coverage of the vascular system and pericytes of MC38 tumors, that is, vascular normalization of the tumors. In the experiment, monotherapy with aPD-1 mAb or RGD-LNP had a relatively small effect on the tumor growth of MC38. However, the combination of mAbs of PD-1 and VEGFR2 knockdown enhanced the infiltration of CD8+ T cells into the tumor, exerting a significant inhibitory effect on tumor growth and improving the response rate. Studies have shown that through combined application, the knockdown of the Vegfr2 in TECs mediated by nanotechnology, enhances the anti-tumor efficacy of aPD-1 mAb immune checkpoint inhibitors[19].
In order to increase photothermal therapy's (PTT) effectiveness, photothermal agents (PTAs) with superior performance are needed to address the issues of light energy inhomogeneity and low conversion efficiency. Zhang, et al. constructed biomimetic nanomaterials (PTA ICG-PEI@HM) using tumor cell membranes (derived from H1975 cells) coated with nanoparticles and polyethyleneimine (PEI) -coupled ICG [20]. Active tumor recognition is achieved through the homologous targeting effect of tumor cell membranes. The nanoparticles are internally connected to indocyanine green (ICG) and PEI through bondsbenzoic acid-imine bond. These chemical bonds are unstable in an acidic environment (pH 5.0-6.8, simulating TME), rapidly breaking and releasing ICG, while remaining stable in a neutral environment (pH 7.4, normal tissue). The ICG release efficiency of nanoparticles was significantly improved under the micro-acidic conditions of the tumor. Bionic targeting ensures the enrichment of drugs in tumors, and ph-responsive release avoids premature drug leakage. The combination of the two enables ICG to accumulate efficiently and be released centrally at the tumor site, enhancing local drug concentration and photothermal efficiency. Combined with the application of PTT, ICG absorbs near-infrared light and generates high temperature, directly destroying the structure of tumor cells. At the same time, NPs induces the generation of ROS and further damages tumor cells through oxidative stress. According to the experiment, the ICG-PEI@HM NPs + laser group's ROS level was noticeably greater than the free ICG group's, and the tumor cell mortality rate reached 82%, while the laser or nanoparticle alone group had limited effect. Nanoparticles ICG-PEI@HM NPS-mediated PTT greatly inhibits tumor growth.

B. Current Research on the Integration of "Diagnosis + Treatment"

Zhang, et al. developed a bionic SPFeNOC with dual targeting of osteoclasts and tumor cells. The surface of SPFeNOC is coated with a mixed cell membrane of cancer cells (4T1 cells) and osteoclasts. Cell membrane encapsulation endows nanoparticles with prolonged in vivo circulation time and excellent biocompatibility[21]. The iron oxide (Fe3O4) nanoparticles and semiconducting polymer (SP) inside SPFeNOC respectively undertake the diagnostic functions of magnetic resonance (MR) imaging and near-infrared (NIR) fluorescence imaging, and at the

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same time participate in the treatment process of chemodynamic therapy (CDT) and sonodynamic therapy (SDT). Integrate the diagnostic and therapeutic functions at the material level. During and after the treatment process, the therapeutic effect can be evaluated again through bimodal imaging to achieve the dynamic combination of diagnosis and treatment and form a complete diagnosis and treatment system (Figure 3)[5].

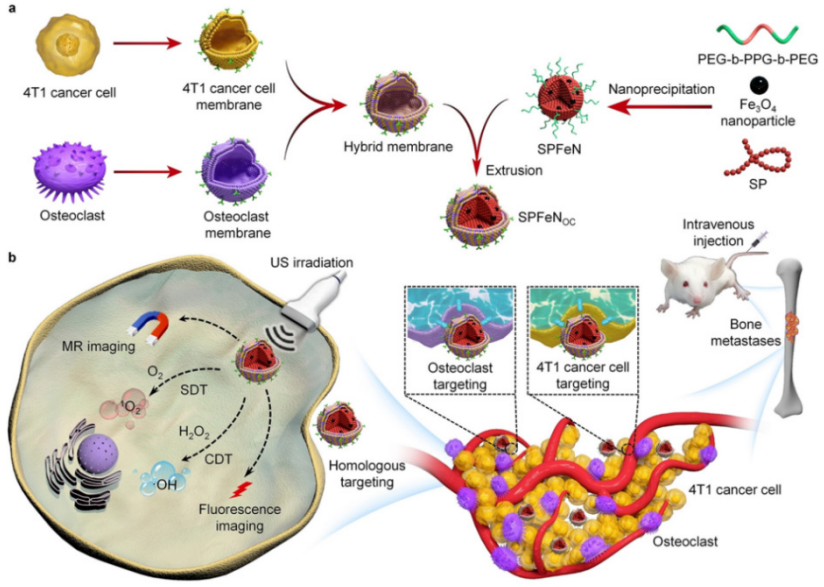

Figure 3. Dual-targeted biomimetic SPFeNOC for amplification therapy diagnosis of bone metastases [5].

IV. 4. Conclusion

At present, modified nanoparticles have been widely confirmed and applied. This article mentions that nanoparticles of different materials, after being modified, can achieve a significant improvement in targeting by using modifiers, such as antibodies, monosaccharides, proteins and other substances that can bind to receptors to achieve targeting. The multi-targeting nanoparticles can simultaneously target tumor cells and tumor support factors in the TME, and the multi-targeting performance can better inhibit the development and metastasis of tumors. Combining nanotechnology with other diagnostic and therapeutic methods can enhance the efficiency of tumor examination and treatment. Moreover, existing studies have simultaneously integrated nanotechnology with diagnostic and therapeutic findings, achieving the integration of tumor diagnosis and treatment. This article provides a theoretical basis for the subsequent development of new nanoparticle modified drugs. It can also develop new paths for treating tumors by combining the characteristics of nanoparticles of different materials with related diagnosis and treatment technologies to achieve a synergistic effect. For example, MNP can be combined with AMF to carry out magnetic hyperthermia therapy, etc. And it provides ideas for subsequent research on combining nanotechnology with related diagnostic and therapeutic methods simultaneously to develop new types of nanoparticles to achieve the integration of "diagnosis + treatment".

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