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Application of nanomaterials in tumor radio-sensitization

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Abstract. Cancer is a main reason of death worldwide, there was about 10million deaths caused by cancer in 2020. Radiotherapy, as a traditional method of treating cancer, uses radiation to kill the lesions of tumor patients. People develop radiation sensitizers to improve the treatment efficiency of radiotherapy and achieve better therapeutic effects through multiple collaborative treatments. Because nanomaterials have special physical and chemical properties, they may bring us novel methods to increase the effectiveness of treatment and reduces damage to the patient's body. People construct nanoplatforms loaded with multiple drugs to achieve a combination of radiation sensitization, toxicity reduction, and biocompatibility enhancement. At present, most nano radiation sensitizers are still in the development stage and have not been put into clinical use. The current research provides potential application prospects, but the existence of toxicity or other side effects cannot be ruled out, and the cost is also a problem that these drugs face before clinical use. This article mainly summarizes some methods of nanomaterial enhanced radiation therapy, research achievements in the past five years, and prospects for future development in this field.

Keywords: nanomaterials; radiotherapy; nano-radiosensitizers.

1. Background

Traditional therapeutic methods for cancer include radiotherapy, chemotherapy, and surgical resection, but these approaches exhibit issues that demand attention, such as easy to recurrence and severe side effect to the body. In recent years, the fields of nanotechnology and biomedicine have been continuously developing, and nanotechnology has helped us overcome the drawbacks of many traditional treatment methods for cancer, such as being more effective and less toxic.

1.1. Brief introduction of current status of RT

The core concept of radiotherapy (RT) involves the application of high-energy ionizing radiation, such as X-rays and γ-rays, which can either directly interact with cellular DNA, causing DNA damage, or indirectly react with water molecules to produce reactive oxygen species (ROS). These ROS then harm DNA and other cellular components, ultimately triggering cell apoptosis and necrosis [1].

However, radiotherapy has many shortcomings that cannot be ignored. According to an assessment conducted at Kenyatta National Hospital, a high proportion of cervical cancer patients experience adverse events [2]. And this survey evaluated the correlation between adverse events and treatment through the Naranjo scale, this study also showed that over 50% of patients with adverse events received radiation therapy, indicating a certain degree of correlation between radiation therapy and physical injury [2].

Radiation therapy cannot be completely targeted and only damages tumor cells, which can cause damage to normal tissues and lead to cell apoptosis. Patients may experience various adverse events such as nausea, diarrhea, or frequent urination. Meanwhile, for oversized tumors, chemotherapy may not be able to eradicate cancer cells, leading to cancer recurrence. For this reason, there is a great need for improvement in this treatment, hoping to improve the accuracy of the treatment and reduce the impact of side effects.

1.2. how can be applied in RT

Generally, most of the nanomaterial-mediated radiosensitization focus on the following three aspects: 1) increase the mortality rate of cancer cells, by enhancing the radiosensitivity of cancer cells or inhibit the repair of damaged DNA in cancer cells; 2) combining with other therapies to enhance the therapeutic effect through the synergistic effect of RT based on nano carriers;3) protecting healthy cells from high energy ionizing radiation [2].

2. Application of nanomaterials in radiation sensitizers

2.1. A general introduction of strategies of nanoradiosensitizers

The goal of most tumor sensitizers is to increase the treatment efficiency of radiotherapy while reducing cell damage caused by radiotherapy. Compared to traditional materials, nanomaterials have unique physical and chemical properties, providing a novel way to achieve the above-mentioned goals.

The common principle for nano radiosensitizers are as follows:

1) High Z nanomaterial can promote energy position in tumor, therefore increase efficiency of treatment. 2) Photocatalytic semiconductor nanomaterials can be stimulated by light to generate free radicals, thereby amplifying the impact of radiation.3) Nanomaterials based on Fe and Cu with chemical catalytic capabilities can facilitate the conversion of H2O2 into toxic HO •, which enhances tumor radiosensitivity. 4) Nanomaterials have the ability to deplete GSH within cancer cells, thereby preventing the neutralization of ROS and enhancing the efficacy of radiotherapy. 5) Nanomaterials capable of elevating oxygen levels within the tumor microenvironment (TME) can effectively counteract tumor hypoxia, resulting in reduced resistance to radiation and the achievement of radiation sensitization. 6) Some nanomaterials enhance their radiation sensitivity by arresting the G2/M phase cells and causing their division process to stop [1].

Currently, nano radiosensitizers are not limited to the use of one of the above methods but are combined with multiple methods to form a diagnostic and therapeutic system that has both diagnostic and therapeutic functions. Nanoplatforms or nanocarriers have a vital role in therapeutic nanosystems, allowing the combination of therapeutic and imaging agents into a unified entity that can perform their functions simultaneously [3].

2.2. Nanoplatforms with specific surface chemical properties for improving tumor microenvironment

The tumor microenvironment consists of non-tumorous stromal cells, tumor cells, and immune cells. Cancer cells engage in interactions with other cells, which makes tumor growth, invasion, and metastasis possible. Therefore, cancer is difficult to treat and prone to recurrence [4]. TMEs involve lower pH (pH 6.5) and higher H_2O_2 concentrations (10-100 μ m). Elevated levels of GSH (2-10 mm) and hypoxia are significant factors in the advancement of tumors [5]. The tumor microenvironment is conducive to the immune evasion of tumors, which poses a substantial barrier to immunotherapy as it hinders the body's immune system from identifying and targeting tumor cells [4].

Some nanoplatforms not only have the effect of radiation sensitization, but also improve the tumor microenvironment, repairing the body's immune system and inhibiting tumor growth.

For instance, Jiang and colleagues developed two nanosystems based on MoSe2, specifically 2D MoSe2 nanosheets (MoSe2 NS) and 3D MoSe2 nanoflowers (MoSe2 NF), each having distinct forms and varying treatment effectiveness. When comparing MoSe2-NS-RGD to MoSe2-NF-RGD, it was observed that the former exhibited superior therapeutic outcomes in several aspects. MoSe2-NF-RGD triggered a higher intracellular overproduction of ROS (Reactive Oxygen Species) and greater mitochondrial damage, resulting in irreversible DNA damage, largely attributed to its stronger photocurrent response under X-ray irradiation. Additionally, MoSe2-NF-RGD demonstrated a preference for targeting and accumulating in mitochondria, which inhibited the expression of selenoproteins, allowing ROS to accumulate in the cellular environment and promoting peroxidation reactions induced by X-ray radiation. Remarkably, when MoSe2-NF-RGD was combined with X-ray therapy, it exhibited a stronger inhibitory impact on the growth of both primary and distant tumors by promoting the infiltration of particular immune cells [6].

Chang et al. synthesized dumbbell shaped NHJs through surface chemical engineering, which is easy to synthesize and has good biocompatibility. Through semiconductor photocatalysis, the dumbbell shaped structure of TeSe NHJs efficiently promotes ROS production and effectively damages tumor cells. Scientists employ cell apoptosis and colony formation assays to investigate the effectiveness of TeSe NDs as enhancers of radiation therapy. It demonstrates significant synergistic effects in radiation therapy and can induce apoptosis in later stages of cell development. Furthermore, when compared to untreated cells and radiation treatments alone, the combination of TeSe NDs and radiation effectively induces G2/M phase cell cycle arrest. The rapid uptake by tumor cells is another strong proof that it is an effective radiation sensitizer. Moreover, TeSe NDs exhibit good TME responsiveness and biodegradability in TME simulated solutions; Combined therapy in the 4T1 mouse break tumor model can efficiently induce more helper T cells to infiltrate tumor tissue and can also trigger a strong anti-tumor immune response, specifically combating tumor progression. In mice, the cooperative impact of X-rays and TeSe NDs-induced immunogenic cell death (ICD) effectively triggers anti-tumor immune responses, albeit with limited duration of efficacy against distant tumors [5].

Undoubtedly, there are still many issues that need to be addressed before these studies are applied in clinical practice. Further research is needed on the detailed mechanisms of these nano platforms combined with radiotherapy in combating tumor progression, and the principles for improving the tumor microenvironment may need to be clarified. In addition, before developing drugs that can be applied, these nanoplatforms require more characterization and functional modifications at the biological level to make the therapeutic effect more stable and effective.

2.3. On Demand Synthesis of Specific Compounds on Nanoplatforms for Tumor Therapy

The limited effectiveness of radiotherapy arises from the low X-ray attenuation coefficient in biological tissues and the subsequent energy loss during radiation delivery to specific tissues, as well as the radiation tolerance of hypoxic tumors. Additionally, tumor cells' DNA repair mechanisms play a role in limiting the effectiveness of radiotherapy. Consequently, there is a desire to decrease the radiation resistance of tumor cells and disrupt DNA damage repair pathways [7].

Liu and colleagues devised a multifunctional system named LRC (LiYF4:Ce@RRS/g-C3N4), loaded onto g-C3N4 nanosheets to enhance radiotherapy through X-ray-induced ONOO generation. This system incorporates a scintillator with a high Z-number (Ce3+) as energy sensors, facilitating the concurrent generation of NO and O2·-. This approach prevents the removal of NO and O2·- by superoxide dismutase (SOD) and oxymyoglobin. The resulting NO and O2·- react to produce ONOO-, which induces lipid peroxidation, disrupts mitochondrial metabolism, and leads to DNA strand breakage, ultimately causing programmed cell death. What's more, this nanosystem can deactivate glutamine synthetase (GS), effectively preventing the reprogramming of nucleotide metabolism via metabolic flux in cancer cells, inhibiting DNA damage repair, and thereby enhancing treatment effectiveness. Additionally, due to its high X-ray attenuation effect, this prepared nanoplatform can also serve as an excellent contrast agent for computed tomography (CT), offering promising applications in both tumor diagnosis and treatment [7].

Through in vivo testing, these nanosystems have demonstrated effective clearance from major organs, mitigating the risk of potential systemic toxicity associated with long-term retention. The administration of LRC in combination with X-ray treatment resulted in mice displaying normal liver and kidney functions, suggesting the suitable biocompatibility of LRC.Furthermore, the combination of LRC and X-ray therapy effectively hinders tumor growth, encourages tumor cell apoptosis, and notably enhances treatment efficacy compared to X-ray therapy in isolation. This presents innovative approaches for tumor treatment employing nanoplatforms, and the findings can be extended to imaging-guided treatment and diagnosis [7].

2.4. Nanoplatforms for imaging-guided diagnosis and treatment

The role of many nano platforms is not limited to treatment, and the development of nano platforms with therapeutic and diagnostic functions that can be used for imaging has become a trend.

Beik and his team developed a versatile nanostructure called GO-SPIO-Au NFs, consisting of graphene oxide nanoflakes (GO NFs) with embedded superparamagnetic iron oxide (SPIO) NPs and AuNPs. This multifunctional platform was designed for localized synergistic cancer therapy. The system leverages the near-infrared (NIR) absorption capability of GO for photothermal therapy (PTT) and the radiosensitization property of AuNPs with the Z element, thereby enhancing radiation therapy (RT). Additionally, the inclusion of SPIO NPs enables the platform to be detectable through magnetic resonance (MR) imaging [8].

In laboratory tests, the nanoplatform demonstrated magnetic resonance (MR) imaging capabilities. After 24 hours of intraperitoneal injection, a decrease in the tumor's MR signal value was observed, indicating the therapeutic effects of the nanosystem. Prussian blue staining verified the existence of iron-rich (SPIO) cells and the efficient internalization of nanoflakes (NFs) within the tumor.In vitro photothermal therapy (PTT) and radiation therapy (RT) experiments revealed that NFs exhibited a catalytic effect on reactive oxygen species (ROS) production, thus enhancing RT. Moreover, NF-induced PTT was observed to initiate the generation of ROS under X-ray exposure, contributing an extra synergistic therapeutic mechanism to the PTT/RT combination. Furthermore, in vitro PTT/RT experiments demonstrated that NFs could inhibit tumor proliferation and metastasis by disrupting tumor blood vessels [8].

Yu et al. reported the research progress of antimony (Sb) and bismuth (Bi) based nanoparticles. Metal nanoparticles have the characteristics of localized surface plasmon resonance (LSPR), which converts light into heat, making it possible for nanoparticles to be used in near-infrared (NIR) laser-driven photoacoustic imaging (PAI) and PTT. In addition, the strong interaction between Sb and Bi elements makes their derived nanoparticles effective radiosensitizers for RT and contrast agents for CT. Bi can form bismuth oxyhalide nanoparticles, compounds, compound-based nanoparticles and Bi-based assembly, which can be applied to cancer imaging and treatment [9]. Pan et al. synthesized cROMP nanoparticles containing Bi, which can enhance CT signals several times in vivo and in vitro. Although this study only conducted experiments on vascular tissue, these nanoparticles have biocompatibility and potential for clinical treatment [10].

Another instance is the work of Sood and colleagues, who developed core-shell nanoparticles composed of iron oxide and gold, decorated with alpha-ketoglutarate. These nanoparticles, referred to as GNP, possess active mitochondrial targeting capabilities. Enhanced radiation sensitivity is achieved by incorporating N-(4-hydroxyphenyl) retinamide into GNP. In addition to their capability for active mitochondrial targeting, these nanoparticles can also serve as highly effective contrast agents for both magnetic resonance imaging (MRI) and computed tomography (CT) [11].

Under 5 Gy gamma radiation exposure, GNP substantially reduces the viability of hepatocellular carcinoma cells. The fundamental molecular process entails the production of reactive oxygen species (ROS) along with a notable elevation in DNA fragmentation. Probes designed to target mitochondria provide confirmation of GNP presence within these cellular structures, potentially contributing to the heightened cellular damage observed. Furthermore, in addition to their active mitochondrial targeting, these nanoparticles, as currently manufactured, can also double as efficient contrast agents for computed tomography (CT) and magnetic resonance imaging (MRI) [11].

Utilizing PLC/PRF/5 liver cancer cells as an in vitro model, GNP demonstrated superior biocompatibility compared to INPs and was found to enhance cell radiosensitivity. However, researchers also observed that these nanoparticles could accumulate in the body, potentially leading to adverse side effects. It is crucial for nanoparticles to be swiftly cleared from the body to prevent toxicity. In in vivo experiments conducted in mice, it was noted that a certain amount of GNP remained in the liver, kidneys, and spleen even after 24 hours of treatment. Among these organs, the liver exhibited the highest level of GNP retention [11].

3. Summary

Based on the above content, nano platform loaded drugs are a relatively effective method for enhancing radiation sensitivity. Most reports have demonstrated the feasibility of nanoplatforms as radiation sensitizers and their multifunctional properties that can combine multiple treatment methods. This provides people with ideas for clinical treatment of cancer, but there is still a lack of evidence on the safety of these drugs and their therapeutic effects and side effects on patients. If these drugs are to be used for clinical treatment, their cost and difficulty in preparation should also be carefully considered. At present, although many nano platforms have good therapeutic effects, their synthesis is complex and their therapeutic effects on model mice are not stable. Therefore, many nanoplatforms still require further research to improve their functionality, perhaps as effective drugs for adjuvant chemotherapy in the future.

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