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Advancements in the Research of Gold Nanomaterials for Radiation Therapy Sensitization

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Abstract

Gold nanomaterials exhibit unique advantages in tumor radiotherapy sensitization due to their enhanced X-ray deposition capability, excellent biocompatibility, and superior chemical, electronic, and optical properties. To date, studies on gold nanomaterial-mediated radiosensitization have been reported, with related mechanisms including catalyzing reactive oxygen species (ROS) production, depleting intracellular glutathione (GSH), overcoming tumor hypoxia, and regulating cell cycles. This article will elaborate on the research progress of gold nanomaterial-mediated tumor radiotherapy sensitization and discuss its mechanisms and future research directions. In addition, the limitations of gold nanomaterials in clinical applications will be further discussed.

Keywords

Gold Nanomaterials, Radiotherapy, Sensitization

1. Introduction

Cancer is one of the leading causes of high mortality worldwide, posing a serious threat to human health. With the rising incidence of cancer, finding effective treatment methods has become increasingly urgent. Among various therapeutic approaches, radiotherapy (RT) is a localized treatment that effectively inhibits tumor growth and is widely used in the treatment of multiple cancers. Radiotherapy works by using high-energy radiation to directly target the DNA of tumor cells, causing double-strand breaks in the DNA, which prevents cells from undergoing normal division and proliferation, thereby achieving a cytotoxic effect. In addition, radiation can interact with intracellular water molecules (H_2O) to generate large amounts of reactive oxygen species (ROS). These ROS induce cell apoptosis or necrosis by damaging DNA, mitochondria, and other cellular structures, further enhancing the efficacy of radiotherapy [1]. However, despite its crucial role in cancer treatment, the inherent resistance of tumor cells and radiotherapy-induced resistance during treatment remain major obstacles to radiotherapy. This resistance diminishes the effectiveness of radiotherapy in killing tumor cells and can lead to tumor recurrence after treatment, resulting in poor patient prognosis [2]. Therefore, to overcome radiotherapy resistance in tumor cells and improve the therapeutic effectiveness of radiotherapy, identifying and developing effective radiosensitizers has become a critical issue in cancer treatment research. In recent years, gold-based nanomaterials, as high atomic number (Z = 79) materials, have attracted increasing attention for their notable radiosensitization properties. Gold nanomaterials exhibit excellent biocompatibility and, due to their easily modifiable surface, can be functionalized with various targeting molecules to enhance their tumor-specific accumulation. Additionally, gold nanomaterials have unique optical and chemical properties, making them ideal radiosensitizers [3]. Gold nanomaterials exhibit diverse mechanisms of action in radiotherapy. They not only enhance tumor cell absorption of radiation by increasing local energy deposition, but also promote ROS generation, which directly or indirectly damages tumor cell DNA. Additionally, gold nanomaterials can lower intracellular glutathione (GSH) levels, thus inhibiting GSH's ROS-scavenging function and allowing ROS levels to rise further, intensifying tumor damage. Moreover, gold nanomaterials can increase oxygen levels in the tumor microenvironment, alleviating hypoxia and improving the efficacy of radiotherapy. By regulating the cell cycle and arresting tumor cells in the radiation-sensitive G2/M phase, gold nanomaterials further heighten tumor cells' sensitivity to radiotherapy. This paper reviews research advancements on the radiosensitization effects of gold nanomaterials, systematically summarizing their multiple mechanisms for enhancing radiotherapy and exploring future research directions and potential limitations in tumor radiosensitization. As a novel type of radiosensitizer, gold nanomaterials demonstrate broad application potential in cancer treatment; however, significant challenges remain for their clinical translation. This study provides a theoretical foundation and research direction for future exploration in this field.

2. Structure and Properties of Gold Nanomaterials

Gold nanomaterials exhibit unique structural and functional properties that make them promising tools in biomedical applications, particularly in cancer therapy. The size, shape, and surface modifications of gold nanoparticles are key determinants of their interactions and behaviors within biological environments [4]. For instance, the electronic and geometric structures of gold nanoparticles play a pivotal role in their catalytic activity, which can be tailored for specific applications such as enhancing radiotherapy effects. Gold nanomaterials are available in various structural forms, including spherical, rod-like, shell-shaped, star-shaped, and nanocage configurations, each providing distinct advantages depending on the therapeutic or diagnostic application at hand [5] [6]. The primary route of administration for gold nanomaterials is intravenous injection, which leverages the enhanced permeability and retention (EPR) effect for targeted tumor accumulation. The EPR effect is a phenomenon observed in tumors, where abnormal and disorganized vasculature and large interstitial gaps allow nanoparticles to permeate more easily and accumulate within tumor tissues. This passive targeting mechanism provides a foundation for gold nanoparticles to accumulate specifically in tumor regions, enhancing their therapeutic efficacy while minimizing off-target effects on healthy tissue [7] [8]. Their biological properties are intimately connected to these structural characteristics. For example, particle size significantly impacts their circulation, biodistribution, and cellular uptake. Studies have shown that gold nanoparticles with a size of around 20 nm achieve optimal tumor accumulation due to their ability to balance effective tissue penetration with prolonged circulation time, while avoiding rapid clearance by the body [9]. Shape also plays a role, as rod-shaped particles may exhibit enhanced cellular uptake or interaction with certain cell types compared to spherical or star-shaped particles. Surface charge further influences cellular internalization; positively charged particles are more readily absorbed by cells due to electrostatic interactions with the slightly negative cell membrane, resulting in improved tumor cell uptake compared to neutral or negatively charged particles [10]. Additionally, targeted surface modifications can be introduced to gold nanomaterials to improve selectivity and retention within tumor tissues. These modifications can include antibodies, peptides, or other targeting molecules that bind specifically to tumor cell receptors, allowing for precise accumulation in the tumor microenvironment. Such targeted functionalization enhances the tumor-specific localization of gold nanomaterials, promoting their retention and effectiveness as a therapeutic agent [11] [12]. Collectively, these favorable characteristics—optimized size, controlled shape, tailored surface charge, and targeted functionalization—form a solid foundation for the application of gold nanomaterials in tumor radiosensitization. By exploiting these properties, gold nanomaterials can enhance the localized effect of radiotherapy, improve therapeutic outcomes, and potentially reduce side effects, making them a versatile and powerful option in the fight against cancer.

3. Experimental Studies on Radiosensitization with Gold Nanomaterials

Early studies mainly focused on the radiosensitization effects of gold nanomaterials. In 2009, Rahman *et al.* found that gold nanoparticles could enhance X-ray-induced cytotoxicity in tumor cells, revealing the potential of gold nanomaterials in radiotherapy [13]. In 2010, Chithrani *et al.* demonstrated that gold nanomaterials could increase local radiation doses and improve therapeutic efficacy [14]. In terms of safety, Hainfeld *et al.* found that gold nanoparticles enhanced radiotherapy efficacy without significant toxicity to normal tissues [15]. In 2013, another study by Hainfeld indicated that gold nanomaterials, besides radiosensitization, could act as imaging agents to improve tumor visualization, further expanding their applications in cancer diagnosis and therapy [16]. In 2017, Soleymanifard *et al.* discovered that thioglucose-modified gold nanoparticles combined with radiation increased DNA damage in human lung (QU-DB) and breast cancer (MCF7) cell lines, providing new insights into gold nanomaterial modifications [17].

In recent years, research on gold nanomaterials in radiosensitization has deepened. In 2020, Huynh *et al.* reported that gold nanomaterials increased localized radiation dose deposition in head and neck tumors, reducing the required therapeutic dose and providing strong evidence for gold nanomaterial radiosensitization [18]. That same year, Yuan *et al.* developed multifunctional peptide-modified ultrasmall gold nanoparticles that selectively accumulated in tumor sites and were rapidly cleared from the body, effectively addressing issues related to nonspecific distribution, slow clearance, and low radiosensitization efficacy of gold nanomaterials [19]. In 2021, Huynh *et al.* found that gold nanoparticles could reduce hypoxia-induced radioresistance in head and neck tumors, thereby enhancing radiotherapy sensitivity [20]. In 2022, Piccolo *et al.* showed that gold nanoparticles combined with radiotherapy significantly increased double-strand DNA breaks in head and neck tumor cells compared to radiotherapy alone, further demonstrating the radiosensitization effect of gold nanomaterials [21].

Multifunctional therapeutic strategies based on gold nanomaterials have been extensively studied. Gold nanomaterials can synergize with various treatment modalities to enhance radiosensitization and improve therapeutic efficacy. In 2020, Safari *et al.* synthesized iron oxide-gold core-shell nanoparticles and demonstrated the synergistic effects of radiotherapy and photothermal therapy in nasopharyngeal carcinoma KB cells, providing a new direction for multimodal gold nanoparticle-based therapy [22]. In 2021, modified iron oxide-gold core-shell nanoparticles loaded with chemotherapy drugs significantly reduced the survival rates of hepatic tumor cells under radiation exposure, offering strong evidence for the combined application of gold nanoparticles, chemotherapy, and radiotherapy [23]. In the same year, composite gold nanoparticles (Au@MC38) that simultaneously enhanced radiotherapy and immune responses strengthened radiation-induced immunogenic cell death [24]. Another study demonstrated that individually encapsulated mesoporous silica-coated gold nanoparticles suppressed tumor cell viability *in vitro* by combining radiosensitization with immunotherapy [25], providing experimental support for the combination of radiotherapy and immunotherapy. Cancer-associated fibroblasts (CAFs) within the tumor microenvironment (TME) promote tumor progression. In 2022, Alhussan's study found that gold nanomaterials could selectively inhibit CAF activity, thereby increasing the number of DNA double-strand breaks induced by radiotherapy, offering a novel approach to cancer treatment [26]. A study found that polyethylene glycol (PEG)-functionalized silver-gold core-shell nanoparticles (PSGNPs) can be used as a radiosensitizer for targeted therapy of glioblastoma multiforme (GBM). This research overcomes the challenge of the blood-brain barrier (BBB) and achieves better radiation therapy efficacy by designing a specific targeted nanoparticle system (TDSGNPs) [27]. Another study suggests that gold nanoparticles, as a multifunctional nanoplatform, combine therapeutic mechanisms such as photothermal therapy (PTT), radiosensitization, and ferroptosis induction. They exhibit efficient photothermal conversion and ROS generation abilities, while also enhancing the effects of radiation therapy [28]. Despite significant progress, the clinical translation of AuNPs as radiosensitizers still faces challenges, necessitating further optimization of nanomaterial design and in-depth investigation of the underlying mechanisms [29].

4. Mechanisms of Gold Nanomaterials in Enhancing Radiotherapy

The mechanisms by which gold nanomaterials act as radiosensitizers significantly enhance their therapeutic effects against tumors. Firstly, gold nanoparticles (GNPs), due to their high atomic number, can effectively damage DNA and organelles in tumor cells by enhancing local energy deposition and generating high-energy electrons, thereby increasing apoptosis rates. Secondly, GNPs promote the production of reactive oxygen species (ROS), which, through oxidative stress, directly or indirectly damage DNA, further increasing the radiosensitivity of tumor cells. Additionally, gold nanomaterials can deplete intracellular glutathione (GSH), inhibiting its role in clearing ROS and thereby elevating ROS levels, which intensifies the damage to tumors. GNPs also improve oxygen levels in the tumor microenvironment, alleviating tumor hypoxia, which enhances the effectiveness of radiotherapy. Finally, gold nanomaterials regulate the cell cycle, prompting tumor cells to enter the G2/M phase, the phase most sensitive to radiation, thus making cells more susceptible to radiation and further enhancing radiotherapy efficacy. These combined mechanisms confer multiple advantages to gold nanomaterials as radiosensitizers in anti-tumor therapy.

4.1. Enhanced Energy Deposition

Gold nanoparticles (GNPs), due to their high atomic number (Z), can significantly increase local energy deposition in radiotherapy, thereby enhancing therapeutic efficacy. When GNPs are exposed to X-ray or proton beam irradiation, secondary electrons (including photoelectrons and Auger electrons) are generated through the photoelectric effect and Compton scattering, resulting in high-density energy deposition within the tumor's localized region. These high-energy electrons effectively damage DNA and critical organelles (such as mitochondria) in tumor cells, thereby increasing apoptosis and improving therapeutic outcomes [30] [31]. Studies have shown that the spatial distribution of GNPs in tumor sites significantly affects the dose enhancement effect. Monte Carlo simulation studies indicate that the localized accumulation of GNPs on tumor blood vessel walls and within blood vessels can markedly increase the local dose, raising the radiation dose in certain areas above the tolerance threshold. This effect may lead to tumor vascular disruption, thereby further increasing the sensitivity to radiotherapy [32]. Additionally, the size and surface modifications of GNPs significantly influence their distribution within tumors and their radiotherapeutic efficacy. Small-sized GNPs (< 50 nm) can take advantage of the enhanced permeability and retention (EPR) effect, allowing for more effective accumulation at tumor sites and prolonged circulation time *in vivo*. Meanwhile, tumor-specific targeting molecules (such as antibodies and peptides) can be used for surface modification of GNPs to increase their tumor specificity and selective deposition, further enhancing radiotherapy efficacy [30] [33].

4.2. Enhancing Energy Deposition and Promoting ROS Generation

Gold nanomaterials possess high-density characteristics, which, when interacting with radiation beams, can increase local photoelectric and Compton scattering effects, thereby enhancing the radiation dose distribution [34]. This interaction generates photoelectrons, Compton electrons, and Auger electrons, which directly act on the cell nucleus to cause DNA damage [35] or indirectly damage DNA by interacting with water molecules to produce reactive oxygen species (ROS) [36]. Among these, DNA damage induced by ROS accounts for the majority of the effects [37]. ROS includes superoxide (O^{2-}), hydroxyl radicals (·OH), hydrogen radicals (·H), protonated water (H_2O+), and hydronium (H_3O+), all of which have high oxidative activity and can cause mitochondrial DNA damage, breaks, and degradation, leading to permanent cellular damage [38]. Additionally, ROS can induce autophagy [39] and antigen presentation by immune cells [40], thereby enhancing the antitumor effects. ROS also reduces Cdc25C protein levels to induce G2/M phase arrest in tumor cells [41], thereby increasing radiotherapy sensitivity. Increasing ROS levels in tumor tissues is crucial for enhancing tumor-killing effects. Gold nanomaterials with smaller diameters and larger surface areas are more effective at interacting with radiation to produce photoelectrons and Auger electrons, thereby generating more ROS and improving radiosensitization [36]. In experiments on melanoma and prostate cancer, the interaction between gold nanomaterials and radiation significantly increased ROS production and enhanced radiotherapy efficacy [30]. In 2022, a study showed that gold nanomaterials promoted excessive ROS generation when interacting with radiation, causing cytoskeletal damage and mitochondrial dysfunction, which significantly improved radiation-induced tumor cell death [42].

4.3. Depleting Intracellular Glutathione Levels

Early studies revealed that depleting glutathione (GSH) enhances the radiosensitivity of squamous cell carcinoma [43]. GSH accounts for approximately 90% of the total intracellular content [44]. GSH is a tripeptide composed of glutamate, cysteine, and glycine. Its active sulfhydryl group (-SH) readily undergoes oxidative dehydrogenation reactions, protecting proteins or other molecules from oxidative stress-induced ROS damage. GSH plays an important role in maintaining intracellular redox homeostasis [45]. Additionally, GSH is a crucial intracellular free radical scavenger that reduces ROS levels and enhances the resistance of tumor tissues to radiation. Reducing GSH levels in the tumor microenvironment is a key factor in increasing radiotherapy sensitivity [46]. Gold nanomaterials undergo strong gold-thiol interactions with intracellular GSH, leading to a reduction in intracellular GSH levels. This interaction may result in GSH depletion within cells, thereby affecting the redox balance and further lowering GSH levels [47]. Studies have shown that using histidine-coated gold nanoclusters (Au NCs@His) as sensitizers can reduce intracellular GSH levels, prevent the generated reactive oxygen species (ROS) from being consumed by GSH, and arrest cells in the radiation-sensitive G2/M phase, thereby enhancing radiosensitivity [48]. In 2017, Yuan *et al.* synthesized a novel gold nanosphere that also demonstrated the ability to promote GSH depletion within tumor cells, enhancing radiotherapy effectiveness [49]. A recent study developed a whole-cell inorganic-biological hybrid system composed of spirulina caps and gold nanoclusters, which enhances cancer radiotherapy through photocatalysis. The system is capable of generating oxygen under light exposure and converting it into superoxide anions, which in turn oxidize glutathione in tumor cells, thereby improving the radiotherapy sensitization effect. Experiments show that this system exhibits superior antitumor efficacy in tumor models and can be rapidly metabolized through biodegradation, demonstrating its potential as a radiotherapy sensitizer [50].

4.4. Improving Tumor Microenvironment Oxygen Levels

The tumor microenvironment (TME) is characterized by hypoxia, low pH, and elevated levels of hydrogen peroxide (H_2O_2) [51]. The mechanisms of tumor hypoxia include restricted blood perfusion, limited oxygen diffusion, and anemic hypoxia [52]. ROS generation is positively correlated with oxygen levels; therefore, a lack of oxygen in tumor tissues leads to reduced ROS production [53] and decreased radiotherapy-induced DNA damage effects [54]. Gold nanomaterials can act as photothermal agents to increase tumor blood flow and improve oxygen levels in tumor tissues, thereby enhancing the radiosensitivity of tumor cells [55] [56]. Furthermore, multifunctional composite gold nanomaterials can produce oxygen under specific stimuli. For example, multifunctional nanoparticles based on MnO_2-$mSiO_2$ hybrid nanocomposites (MNHs) and gold nanoparticles (AuNPs) (MAHNPs) can decompose endogenous H_2O_2 in tumors to produce oxygen, thereby increasing oxygen levels in the tumor microenvironment and enhancing radiotherapy efficacy [57]. Additionally, studies have shown that using porphyrin-metal-organic frameworks (MOF)-gold nanoparticle hybrids with catalase-like activity can increase oxygen levels in tumor tissues and enhance radiotherapy effectiveness [58]. Researchers have developed a two-dimensional Pd@Au core-shell nanostructure (TPAN) that continuously catalyzes H_2O_2 to generate oxygen, effectively overcoming tumor hypoxia over the long term [59]. These studies suggest that gold nanomaterials may help increase oxygen levels in the tumor microenvironment, thereby offering new possibilities for cancer treatment.

4.5. Regulating the Cell Cycle

The cell cycle consists of four stages: G1, S, G2, and M. Among these, the G2/M phase is the most radiosensitive, while the S phase is the most radioresistant. Therefore, gold nanoparticles that block tumor cell cycle progression at the G2/M phase can enhance radiosensitivity. Studies have found that drug-encapsulated gold nanoparticles can induce cell cycle arrest by altering DNA conformation and regulating cell cycle-related proteins [60]. Gold nanomaterials (AuNPs-si-SP1) have been shown to decrease the expression of specificity protein 1 (SP1), promoting tumor cells to enter the G2/M phase and increasing the ability to induce DNA double-strand breaks under radiation [61]. Studies have demonstrated that gold nanomaterials combined with radiotherapy can induce melanoma cell cycle rearrangement, increasing the proportion of cells in the radiation-sensitive G2/M phase [62]. Glucose-capped gold nanoparticles can induce the activation of CDK kinases, leading to accelerated transition from the G1/S phase to the G2/M phase, increasing the inhibitory effect of radiation on tumor cells by 1.5- to 2-fold [63]. In 2020, Tabei *et al.* synthesized folic acid-conjugated gold nanoparticles that induced nasopharyngeal carcinoma KB cells into the highly radiosensitive G2/M phase, thereby enhancing radiotherapy efficacy [64].

5. Gold Nanoparticles in Synergistic Radiosensitization with Multiple Therapeutic Approaches

Gold nanomaterials possess various properties that make them highly promising in cancer treatment applications. Their exceptional radiosensitizing effects, high surface area, and excellent biocompatibility allow them to efficiently accumulate within tumor tissues and enhance therapeutic efficacy. Additionally, gold nanomaterials exhibit high photothermal conversion efficiency, enabling them to destroy tumor cells through photothermal therapy. Their strong X-ray attenuation capacity allows them to effectively absorb radiation and transfer this energy to tumor cells. Furthermore, gold nanomaterials possess a good drug-loading capacity, enabling them to carry a range of therapeutic drugs and biomolecules to enhance radiotherapy outcomes.

Gold nanoparticles can be loaded with radiotherapy-sensitizing agents, such as chemotherapy drugs, photothermal transduction agents, photosensitizers, immunoadjuvants, and genetic materials. These agents can work synergistically with radiotherapy through various mechanisms. For example, chemotherapy drugs can damage the DNA of cancer cells, increasing their sensitivity to radiotherapy; photothermal transduction agents can generate heat under near-infrared light to further destroy tumor cells; photosensitizers produce reactive oxygen species (ROS) under light exposure, exerting toxic effects on tumor cells. Meanwhile, immunoadjuvants and gene therapy agents can modulate the tumor microenvironment, enhancing the immune system's ability to attack tumors. This combined treatment strategy enables the synergy of multiple therapies mediated by gold nanomaterials (such as photothermal therapy, photodynamic therapy, chemotherapy, and immunotherapy) with radiotherapy, significantly improving the effectiveness of cancer treatment.

5.1. Gold Nanoparticles in Synergistic Photothermal Therapy and Radiosensitization

Photothermal therapy (PTT) combined with radiotherapy (RT) is an effective cancer treatment strategy that can reduce radioresistance and induce tumor-specific apoptosis or necrosis [65]. Due to their efficient photothermal conversion capability and good biocompatibility, gold nanoparticles serve as ideal carriers for PTT. Studies have shown that radioactive iodine-131-labeled gold nanoframes combined with second near-infrared light effectively inhibited subcutaneous breast tumors in mice, demonstrating greater efficacy than radiotherapy alone [66].

Highly thermosensitive gold nanocages under irradiation exhibited high photothermal conversion efficiency, inducing tumor cell death [67]. Another study showed that the combined treatment of photothermal therapy and radiotherapy effectively alleviated tumor radioresistance and induced tumor-specific apoptosis and necrosis, achieving a 96.6% tumor inhibition rate. Thus, this combined therapeutic approach holds significant efficacy for deep-seated malignancies and shows promising potential for clinical impact [68]. The latest study proposes a gold-modified magnetic vortex donut (GMVD) as a multifunctional nanoplatform that combines therapeutic mechanisms such as photothermal therapy (PTT), radiosensitization, and ferroptosis induction. GMVD exhibits efficient photothermal conversion and ROS generation abilities, enabling the induction of ferroptosis in tumor cells under 808 nm laser irradiation, while also enhancing the effects of radiation therapy. Through the synergistic effect of photothermal therapy and radiation therapy, GMVD significantly improves tumor ablation efficacy, demonstrating its great potential in tumor diagnosis and treatment, with good biocompatibility and antitumor efficacy [28].

5.2. Gold Nanoparticles in Synergistic Chemotherapy and Radiosensitization

In studies on the radiosensitization effects of gold nanoparticles (AuNPs) combined with chemotherapy and radiotherapy, AuNPs have shown significant potential to enhance radiotherapy. For example, when AuNPs are used in conjunction with chemotherapeutic agents like cisplatin, they can substantially increase DNA damage in tumor cells, thereby inducing a higher apoptosis rate through radiotherapy [69]. Additionally, research by Tingting Li found that polyethylene glycol (PEG)-modified AuNPs combined with the chemotherapeutic drug doxorubicin (DOX) significantly inhibited tumor cell proliferation under radiation activation. This combination therapy demonstrated radiosensitization effects in both *in vivo* and *in vitro* experiments [70]. In 2022, Luan *et al.* designed an aggregated gold nanoparticle system loaded with doxorubicin, which enhanced radiation-induced DNA damage, apoptosis, and cell cycle arrest [71]. A recent study showed that the combination of gold nanoparticles (GNP) and docetaxel (DTX) in both *in vitro* and *in vivo* radiotherapy (RT) significantly reduced tumor spheroid size and increased DNA double-strand breaks (DSB), while also reducing tumor growth and extending the median survival time of mice after treatment [72]. The combination of gold nanoparticles with chemotherapeutic drugs achieves greater anticancer effects. This combined strategy holds promise for providing substantial advantages in the treatment of deep-seated tumors.

5.3. Gold Nanoparticles in Synergistic Immunotherapy and Radiosensitization

The combination of gold nanoparticles with immunotherapy can significantly enhance therapeutic efficacy. Gold nanoparticles can release antigens, oligonucleotides, adjuvants, and immune stimulators, serving as an effective therapeutic strategy with low toxicity, improved targeting, and enhanced cellular uptake rates [73]. Additionally, gold nanoparticles can combine with immunotherapy to induce immunogenic cell death, thereby markedly enhancing radiotherapy-induced immunogenic cell death. Studies have shown that combining gold nanoparticles with radiotherapy significantly improves immunogenic cell death effects in glioblastoma cells. This combined therapy also promotes the release of key damage-associated molecular patterns (DAMPs) such as CRT, HMGB1, and ATP [74]. The combination of gold nanoparticles and radiotherapy also promotes immune cell infiltration, enhancing radiotherapy-induced immunogenic cell death [75]. A study found that after M-Au@RGD-NM combined with RT treatment, M-Au@RGD-NM significantly activated the STING pathway, modulated systemic immune responses, promoted dendritic cell maturation, upregulated CD8 T cells, and induced M1 polarization. Additionally, it induced CD8 T cell infiltration in distant tumors, resulting in significant antitumor effects, enhanced radiotherapy efficacy, and immune response activation through the STING pathway. This provides new insights into radiosensitization and immunotherapy [76]. This combined treatment strategy helps activate the immune system, enhancing the immune response against tumors and thus improving therapeutic outcomes.

5.4. Gold Nanoparticles in Synergistic Gene Therapy and Radiosensitization

The application of gold nanoparticles in gene therapy for radiosensitization primarily involves enhancing tumor cell radiosensitivity through gene silencing. For example, specific types of gold nanoparticles can carry antisense oligonucleotides (ASON) against survivin mRNA to target and silence the survivin gene. Survivin is an anti-apoptotic protein highly expressed in various tumors, and gene silencing to inhibit its expression can significantly increase the radiation sensitivity of tumor cells. In practical applications, pH-responsive gold nanocluster polymers release antisense oligonucleotides in the acidic tumor microenvironment, activating the silencing of survivin at the tumor site. Experimental studies have shown that this approach effectively enhances radiosensitization, increasing tumor cell radiosensitivity by approximately 1.81 times [77]. This gene-silencing strategy has demonstrated effects in various cancer cell lines, enhancing oxidative stress responses and inhibiting tumor cell proliferation [78]. Other studies have indicated that mesenchymal stem cell-mediated gold nanoparticles combined with the hNIS gene can improve the radiotherapy efficacy against tumor tissue [79]. In summary, the use of gold nanomaterials to deliver antisense oligonucleotides against survivin promotes the synergistic effects of radiotherapy and gene therapy through multiple mechanisms, providing new avenues for the future application of nanogene therapy in cancer treatment.

6. Discussion

Gold nanomaterials are excellent radiosensitizers, with current research primarily focused on leveraging their properties to develop multifunctional nanoplatforms that expand their applications in clinical radiosensitization studies. Despite their strong potential in enhancing radiotherapy, gold nanomaterials still face challenges in clinical application. Firstly, the nanostructure, size, charge, and surface modifications of gold nanomaterials significantly impact their biodistribution, tumor targeting, and clearance rate *in vivo*. Optimizing the structure and physicochemical properties of nanoparticles to improve therapeutic efficacy requires further investigation. Additionally, the toxicity and metabolism of gold nanomaterials in the human body are not yet fully understood, and oxidative stress and inflammatory stimuli induced by nanoparticles have certain cytotoxic effects on both tumor and normal cells. The prolonged retention of gold nanomaterials in the body may lead to potential toxicity accumulation, especially in major organs such as the liver and kidneys. Ensuring good biocompatibility and safety while maximizing therapeutic efficacy is crucial for future development. Moreover, challenges such as tumor microenvironment heterogeneity, drug resistance, and immunosuppression still limit the radiosensitization effects of gold nanomaterials to some extent, and addressing these microenvironmental complexities remains a key challenge.

6.1. Future Research Directions Could Focus on the Following Aspects

6.1.1. Enhancing Tumor Targeting and Selectivity

In order to further enhance the targeting and selectivity of gold nanomaterials within tumors, techniques such as genetic engineering and targeted ligand modification can be utilized. By modifying the surface of gold nanomaterials with specific ligands, such as antibodies, peptide chains, or other tumor-targeting molecules, these nanomaterials can more effectively recognize and accumulate in tumor areas, minimizing effects on normal tissues and maximizing radiosensitization. Genetic engineering techniques can also be employed to design nanoparticles with unique functions, allowing responsive release to specific tumor cells or microenvironments, thereby boosting their targeting ability and enhancing overall therapeutic effectiveness.

6.1.2. Multifunctional Nanoplatform Construction

Exploring the construction of multifunctional nanoplatforms by combining gold nanomaterials with other therapeutic approaches—such as chemotherapy, immunotherapy, and gene therapy—can achieve multimodal, synergistic treatment. The combined use of radiotherapy and chemotherapy can accelerate DNA damage in tumor cells, while radiotherapy coupled with immunotherapy helps activate the immune system, strengthening long-term tumor suppression. By using gold nanomaterials as carriers that deliver multiple therapeutic drugs and biomolecules, this approach can overcome the limitations of single therapies, achieving more effective comprehensive treatment, especially in managing deep-seated or recurrent tumors with significant potential.

6.1.3. *In Vivo* Distribution and Toxicity Studies

There is a need for systematic studies on the *in vivo* distribution and long-term toxicity of gold nanomaterials. Although current studies indicate that gold nanomaterials possess good biocompatibility, the possibility of their long-term retention in the body remains. Research on *in vivo* distribution and toxicity is critical for the clinical application of nanomaterials and helps optimize their design and application, ensuring their safety in the human body. Future studies should focus on aspects such as metabolic pathways, organ distribution, and long-term side effects of gold nanomaterials to establish a more comprehensive and reliable toxicological evaluation system. Additionally, developing more efficient pathways for nanomaterial metabolism and excretion, such as by improving controlled degradability and clearance rates through surface modifications, will help minimize adverse reactions to the greatest extent possible.

7. Conclusion

In conclusion, gold nanomaterials hold great potential for application in enhancing radiotherapy for tumors and possess significant value for clinical translation. However, to achieve successful transition from the laboratory to clinical application, continued in-depth exploration is needed in both basic and applied research. By further investigating the radiosensitization mechanisms of gold nanomaterials and conducting thorough and systematic studies on their biological safety, significant breakthroughs in the clinical application of gold nanomaterials in tumor treatment can be anticipated. With continuous technological advancements, gold nanomaterials are expected to offer new hope for enhancing radiotherapy and comprehensive cancer treatment, providing cancer patients with more effective and precise therapeutic options.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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