ROLE OF GOLD NANOPARTICALS IN CANCER THERAPY

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ABSTRACT:Cancer remains a major global health problem that requires innovative treatment strategies. Gold nanoparticles (PNBs) have become promising tools in cancer therapy due to their unique physicochemical properties. Their tunable size, shape and surface chemistry offer versatile functionalities that can be tailored for specific applications in cancer therapy. The purpose of this summary is to highlight the central role of MEP in various aspects of cancer treatment. GNPs have shown tremendous potential in drug delivery by improving the efficacy of conventional chemotherapy agents by improving their solubility, stability, and targeted delivery to tumor sites. In addition, their ability to absorb and convert near-infrared light into heat (photothermal therapy) enables precise local destruction of the tumor while minimizing damage to healthy tissue.

In addition, GNPs have been important in diagnostic imaging techniques such as computed tomography (CT) and photoacoustic imaging. , which makes it possible to detect cancer at an early stage and accurately monitor treatment responses. Their use in combination therapy, such as photodynamic therapy and radiosensitization, has shown synergistic effects, increasing treatment results. Despite these promising advances, GDP and #039 optimization still have challenges; ensuring biocompatibility, pharmacokinetics and long-term safety profiles. Addressing these issues will pave the way for the clinical translation of GNP-based therapies, providing new opportunities for personalized and effective anticancer treatment. The versatile applications of gold nanoparticles in cancer therapy offer enormous potential to change the landscape of cancer treatment by providing targeted, precise, and minimally invasive therapeutic procedures. Further research and development in this area promises to bring these new strategies from the laboratory to the clinic, ultimately benefiting cancer patients worldwide.

KEYWORDS: Gold nanoparticals, cancer therapy, Drug Delivery, Tumor,AuNPs

INTRODUCTION

Cancer is the general term for a group of genetic diseases characterized by unrestricted random cell division and invasiveness. Cancer development is mainly caused by mutations or changes in the expression patterns of proto-oncogenes, tumor suppressor genes, and genes involved in DNA repair. Disruption of pro-apoptotic signaling and overexpression of many proteins that promote cell growth and additional nutrients hinder the development of effective cancer therapies. Most cancers are caused by environmental factors such as exposure to radiation and pollution, but the most important are unhealthy lifestyles such as lack of exercise, poor diet, smoking and stress. Only 5-10% of cancer cases are related to inherited genetics. The risk of cancer increases significantly with age, and many of these diseases are more common in developed countries.[1]

Cancer, the uncontrolled growth of cells, is a deadly disease that affects many people around the world. Cancer is the most common cause of death in all countries of the world in the 21st century.[2] According to the World Health Organization (WHO), cancer killed 10 million people in 2020, making it the leading cause of death worldwide. Cancer deaths are expected to increase worldwide, with an estimated 12 million cancer deaths in 2030. Therefore, the boundaries of cancer research are constantly being challenged to develop the most effective tools for cancer diagnosis, monitoring and treatment.[3] Cancer is a great threat to people's health and quality of life.[4] Therefore, it is an ongoing challenge to develop effective methods for cancer diagnosis, monitoring and treatment.[5]

Cancer treatment is determined by the type of cancer, the stage of diagnosis and the patient's ability to withstand the given treatment. In general, the stages of cancer can be classified as early, middle or late.[6] Currently, surgery, chemotherapy and radiation therapy are used to treat cancer. Although these methods have been accepted and used for decades, they have disadvantages and side effects. For example, surgical removal of tumors is mostly limited to large, resectable and easily accessible tumors. Chemotherapy drugs target only rapidly dividing cells and thus not only kill cancer cells, but also destroy normal cells such as bone marrow cells and immune cells.[5] This causes widespread "collateral damage" throughout the patient's body. Radiotherapy involves the use of high-energy radiation (such as X-rays and gamma rays) to destroy tumor cells and inevitably causes damaging effects on healthy tissues in the radiation path. Given the shortcomings of current therapies, one important goal of improving cancer therapy is to target therapeutic agents specifically to tumor cells while sparing healthy tissue from tumors.[3]

Considering all these aspects, there is a great need to develop new strategies for effective diagnosis and treatment of cancer. In recent years, the extraordinary growth of research and applications in the field of nanotechnology and nanoscience has brought hope to avoid the shortcomings of classical cancer treatment.[1] The term nanotechnology encompasses the study and application of particles measured on a scale of one billionth of a meter. The particles, called NPs, can be groups of ions, atoms or molecules within a certain size range of 1-100 nm. Although the size can vary depending on the application, for example, NPs synthesized for drug delivery are usually larger than 100 nm to allow for the delivery of a good amount of drug. Also, for cancer therapy, the ideal size of NPs is 70-200 nm, because the fenestrations of the developing tumor endothelium are about 200-780 nm. In the laboratory, they can be synthesized by various methods - abundant physical-chemical and biological sources - chemical substances, polymers, proteins, plants, microbes, etc. NPs can be classified by type – polymeric, metallic, magnetic, carbon nanotubes, liposomes, dendrimers and quantum dots. These NPs exhibit unique optical, magnetic, electronic, and catalytic properties that differ from their micro- and macro-counterparts. The extensive use of different sources and methods leads to the synthesis of a wide variety of NP products, which can be used in the production of biosensors and electrochemical sensors, sewage treatment, forensic medicine, currency, hologram printing, and more important biological and medical applications. As a result, the many advantages and many applications of NPs in various fields have led to the unregulated growth and development of the field of nanotechnology, causing the expansion of nanopollution now more than ever. As the saying goes, "with great power comes great responsibility" - we need to develop rules and regulations to assess the effects of synthesized NPs on human health and the environment.[7]

Among the many nanomaterials being developed for nanomedical applications, this review focuses on gold nanoparticles (AuNPs) and their potential as tumor sensors, drug delivery agents, and enhancers in plasmonic photothermal therapy for cancer eradication. In this review, we specifically focus on ultrasmall gold nanoparticles (GNs) with diameters below 10 nm. We first discuss the methods of synthesis and surface functionalization of ultrasmall GNs. The use of ultrasmall GNs in cancer diagnostic imaging is briefly reviewed. Applications of ultrasmall GNs in cancer therapy, including photothermal therapy, gene therapy, radiation therapy, etc., are further discussed. This information can be important for the further development of clinical applications of GNs. The use of AuNPs is gaining popularity in these fields of research for several reasons. First, AuNPs are considered to be relatively biologically unreactive and therefore suitable for in vivo applications compared to the highly toxic cadmium and silver NPs, although several groups (as explained in later sections) challenge this view. Other favorable features include the strong optical properties of AuNPs due to the localized surface plasmon response (LSPR), the easily tunable surface chemistry that allows versatile incorporation of surface functional groups, and finally the ease of controlling particle size and shape during synthesis. AuNPs can be considered fully multifunctional, with the potential to combine various desired functions in a single molecular package. All these factors contribute to the high interest and preference for the use of AuNPs over other NPs. Examples of other nanomaterials for biomedical applications can be found in other published articles on the use of quantum dots, functionalized fullerene-based nanomaterials, and magnetic NPs in the diagnosis and treatment of human diseases.[3]

Historical details of gold nanoparticles

Gold nanoparticles were first described by Michael Faraday in 1857. He described the synthesis of multicolored solutions by reacting gold chloride with sodium citrate. Since then, gold nanoparticles have been used to fulfill scientific and medical requirements. In the 1950s, the discovery of particles that bound to biological proteinaceous substances without changing their function paved the way for their use in immunodiagnosis and histopathology. Recently, gold nanoparticles have been assembled into scaffolds for use in DNA diagnostics and biosensors. Colloidal gold nanoparticles have been used in the treatment of rheumatoid arthritis and radioactive gold nanoparticles in the treatment of cancer.

About 50 years after their description as antineoplastic agents, colloidal gold nanoparticles are re-rising as main applicants withinside the subject of tumor-focused nano remedy. Hirsch et al defined using colloidal gold nanoshells (composed of aminated silica middle particle, studded with 1-three nm gold debris) for the thermal ablation remedy of strong tumors. These debris while uncovered to mild source (diode laser) with the wavelength of 820 nm, excites the electrons gift at the floor of gold, ensuing in particle heating. Interstitial injection of those debris close to the tumor observed with the aid of using laser mild excitation brought about a considerable discount of transmissible venereal tumors.[8]

GOLD NANOPARTICLES AS DRUG CARRIERS

Traditional methods of administering chemotherapy drugs, i.e., oral or intravenous administration, result in drug distribution throughout the body, with only a portion of the drug reaching the tumor site. However, it can have adverse effects on healthy tissues and organs. This problem of side effects is avoided by targeted drug delivery methods, which can be defined as a process in which a certain biologically active compound or drug is released in a controlled manner at a specific location. Because of their small size, they can efficiently pass through capillaries to reach their target cells. The fact that chemotherapy drugs can be loaded or attached to nanoparticles has opened up enormous possibilities for drug delivery. Because of their small size, they can efficiently pass through capillaries to reach their target cells. Chemotherapy drugs can be loaded or attached to nanoparticles and can be directed either passively or actively to the tumor site. Tumor tissue typically has a leaky vasculature that allows nanoparticles to easily accumulate. This is also known as the enhanced permeability and retention (EPR) effect. This form of passive targeting exploits the pathophysiological characteristics of the tumor tissue. However, this approach has some limitations, including indiscriminate targeting and inefficient distribution of drugs into tumor cells. In addition, not all tumors have the EPR effect. In active targeting, tumor-specific biomarker ligands such as monoclonal antibodies, aptamers, peptides, and vitamins are conjugated to the nanoparticle surface. These ligands then interact with tumor cell receptors, allowing endocytosis and subsequent drug release. Thus, active targeting provides a higher probability of endocytosis compared to the passive targeting method. Gold nanoparticles have attracted the attention of researchers for their use as drug carriers due to their SPR, optical, and tunable properties. They can be made in several different core sizes (1-150 nm), which makes it easy to control their dispersion. The negative charge on the surface of gold nanoparticles makes them easily transformable. This means that they can be easily functionalized by adding various biomolecules such as drugs, targeting ligands and genes. In addition, the biocompatibility and non-toxic nature of gold nanoparticles make them excellent candidates for use as drug carriers.[9]

BASIC CHARACTERISTICS OF GOLD NANOPARTICLES

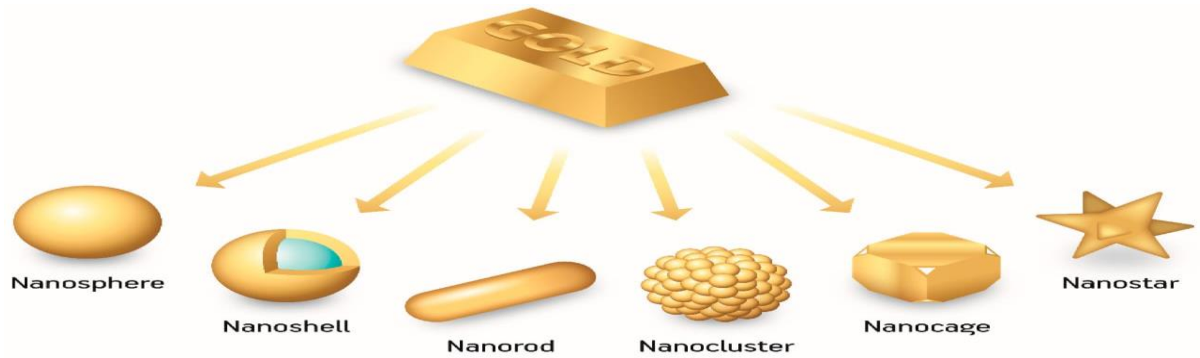
To understand how Au NPs can be effectively incorporated into a basic science or clinical research protocol, we first examine the properties of Au NPs and how these properties help us address the clinical need for more targeted delivery of anticancer drugs. Au NP size, shape, charge, toxicity and biocompatibility are investigated.[10]

Size of gold nanoparticles

In general, NPs are man-made particles ranging in size from a few nanometers to about a few hundred nanometers in the narrowest two dimensions. The size of Au NPs can have several potentially competing effects on their use in cancer therapy. The size of a NP determines its physical properties and surface area, such as the color of the NP, and even affects how the body interacts with the NP. One of the main reasons to consider the use of NPs in cancer therapy is the ability to operate the Au NP and selectively deliver the drug only to the tumor region. Both Au NP functionalization and drug delivery require the drug and the functionalizing agent to attach to the surface of the top layer or top layer.

Shape of gold nanoparticles

Au NPs can be prepared in the form of solid spheres, shells, cages, rods, chains and stars. Like NP size, shape affects surface area, i.e., how the body interacts with the NP, and NP color. Currently, solid spheres, nanorods (Au NPs that are narrow in two dimensions and longer, 100 nm, along the third dimension) and nanostars (very symmetrical, star-shaped Au NPs) are of greatest interest. For spherical Au NPs, because the NPs are symmetrical in three dimensions, the surface plasmon resonance is single-valued, and the light absorption, reflection, and transmission behavior of Au NPs is also single-valued. Because gold nanorods are symmetrical along two axes but longer along a third axis, gold nanorods exhibit bimodal (transverse and longitudinal) surface plasmon resonance behavior—the longitudinal mode of gold nanorods corresponds to the longer wavelength of NP light absorption. Generally, Au NPs are designed to have an infrared absorption peak (longitudinal mode). Near-infrared wavelengths penetrate tissues much more than visible light and are used in photothermal therapy.[13]

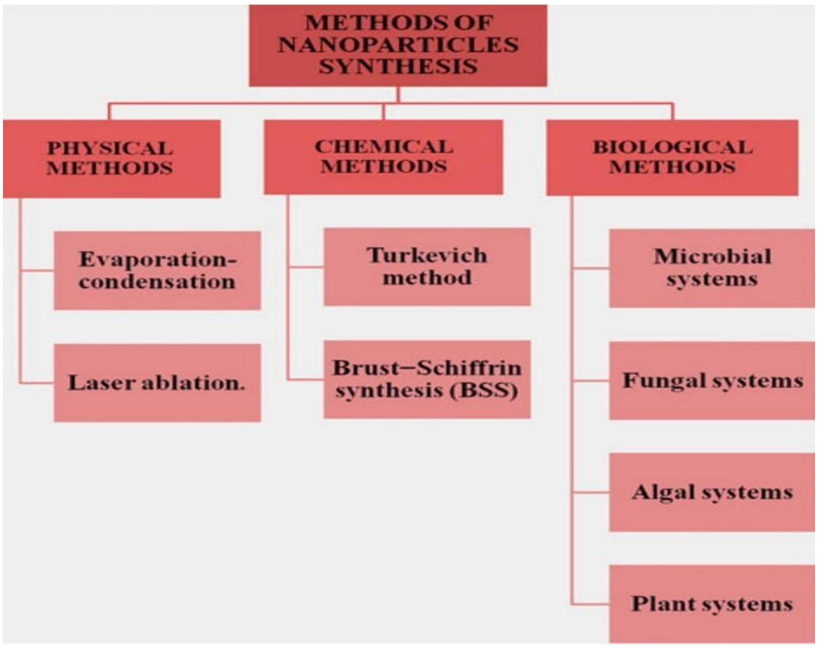


Charge of gold nanoparticles

In order for AuNPs not to aggregate in solution, they must have positive or negative electrical charges that repel each other, but still remain soluble. The surface charge in an NP is described by its zeta potential (quantity of the electric potential on the surface of the NP relative to a distant, uncharged region). Uncoated AuNPs must have a zeta potential of at least 20 mV to remain stable in solution. The zeta potential of AuNPs must be carefully chosen on a case-by-case basis based on the coating parameters. If you want a positively charged molecule (or the positive end of a bipolar molecule) to bind to an AuNP, you must use AuNPs with a negative potential to attract the positive molecules or the positive ends of the bipolar molecule.[14]

SYNTHESIS

In general, synthesis can be classified into top-down and bottom-up methods. The bottom-up method involves building NPs from molecules or atoms, while the top-down methods involve dividing bulk materials into smaller particles that ultimately result in NPs.[15] However, it is easier to divide the synthesis routes of metal NPs into physical, chemical and biological.



GENERAL FORMATION OF NANOPARTICLES IN SOLUTIONS

It is important to understand the synthesis mechanism of NPs in solution, because it is affected by different parameters and conditions placed during the reaction. A better understanding of the mechanism would lead to optimization of the synthetic protocol to achieve NPs with a certain size distribution and other related - surface, optical properties, etc. The mechanism involves about five different processes in a sequential sequence - reduction, nucleation. , growth, roughening and agglomeration. Once the metal salt is reduced, nucleation begins. In its simplest form, nucleation is the process by which atoms form small clusters called nuclei, which act as a template for the formation of NPs. Nucleation can be both heterogeneous and homogeneous; homogeneous nucleation occurs spontaneously and randomly, but supersaturation is a prerequisite. Supersaturation is the initiation and growth of soluble nuclear species, which can be achieved by dissociating or reducing soluble salts to metal atoms. On the other hand, heterogeneous nucleation occurs only where the solid surface is in contact with the liquid surface.

A correct theory must explain and deduce the difference between the two phases, nucleation and growth; it is explained by the splash theory of LaMer and is thus the most widely used theory in the general mechanism of NP synthesis. This theory states that during synthesis, the concentration increases rapidly above saturation for a short time, followed by nucleation, resulting in multiple small nuclei. A time-differential phase occurs when these established nuclei grow further, lowering concentration levels well below nucleation. During the growth phase the necessary decrease in surface energy occurs. Smaller particles have a high surface-to-volume ratio and thus a higher surface energy,

Which makes them thermodynamically unstable, because these particles grow due to monomer diffusion at the surface interface, the surface energy decreases and the resulting larger particles are thermodynamically stable. As diffusion continues, the particles grow; particles survive only if their radius is above a critical value, otherwise they dissolve back into the solution. Over time, the monomer concentration decreases, leading to the formation of larger NPs at the expense of smaller NPs, i.e., the smaller NPs redissolve and add mass to the growth of larger particles. This process of greater formation is called hardening or Ostwald ripening. This phase change process, which leads to an increase in size and a wide distribution of particle sizes in solution. The size distribution is narrow in the early stages of growth when the building material concentration is high, leading to monodispersity, but widens as the concentration decreases, leading to Ostwald ripening, an increase in mean size, and solution polydispersity. Another consequence of this process is morphological changes when the small nuclei disappear and dissolve to form larger particles in the two-phase system. Perhaps the last of all processes, agglomeration is defined as a reversible step in which weak physical forces, such as Vander Waals forces, hold particles dispersed in solution close together. This is due to a further decrease in surface energy and more thermodynamically stable particles. Suspended particles in solution can also come together; there is a difference between agglomeration and aggregation - agglomeration is irreversible and agglomeration is a reversible process.

This part of the process is undesirable because it reduces the concentration of NPs in the solution, so additional steps must be added to the procedure to prevent agglomeration or aggregation of NPs. This step to prevent agglomeration or aggregation is called NP stabilization and is important for their successful application in various fields.[25]

THE ROLE OF GOLD NANOHAIRS IN THE TREATMENT OF SPECIAL CANCER

In this section, recent advances in the use of AuNPs in the treatment of various cancer types are broken down by organ system. Although not a comprehensive treatment for all organ systems or cancer types, it provides insight into ways in which the properties of AuNPs can be used to develop more precisely targeted and effective cancer therapies. Applications of AuNPs generally fall into one of three, often complementary, categories: targeted delivery of a chemotherapeutic agent, enhancement of radiation/thermotherapy, and contrast enhancement in in vivo tumor imaging.

Reproductive organ cancer

Currently, AuNPs have been widely studied in the treatment of prostate and breast cancer, the two most common types of cancer in men and women. The earliest approaches to the use of AuNPs in the vicinity of the tumor, resulting in rapid local attenuation of radiotherapy gamma rays and ultimately increased radiation dose delivery to the tumor region. Although this approach has been shown to be effective in increasing radiation dose in some cases, the consensus of the medical physics community is that the wide range of size, shape, charge and coating makes general statements about the effectiveness of AuNPs difficult. in radiation enhancement. . therapeutic dose. Furthermore, to maximize the radiation dose-enhancing effect of AuNPs, a more targeted approach that maximizes the uptake of AuNPs into tumor cell nuclei is needed.

Most studies on the effectiveness of AuNP-based cancer therapies in reproductive cancers focus on the targeted delivery of chemotherapy drugs. In these studies, AuNPs are usually conjugated with a targeting agent and loaded with at least one chemotherapy drug.

Cancer of the central nervous system

Brain tumors (gliomas) are the most lethal tumor subtypes, because tumor location, grade, histopathology, and recurrence have a decisive influence on patient survival. Poor penetration of therapeutic drugs into the central nervous system (CNS) is largely due to the blood-brain barrier (BBB), which limits treatment options for neurological diseases such as brain tumors. The BBB is a specialized semipermeable membrane barrier composed of capillary endothelial cells that line the cerebral microvessels and surrounding perivascular elements. The unique tight junctions between endothelial cells are very effective in limiting access to the CNS. The BBB structure allows passive diffusion of only gases, water and hydrophobic molecules with a molecular weight of less than 400-500 Da. Other nutrients and endogenous molecules such as amino acids, glucose, vitamins or essential fatty acids must be actively transported across the membrane by transporters found at the BBB. In addition, the BBB is a metabolic barrier because it contains enzymes that metabolize and inactivate toxins, neuroactive compounds, and chemotherapeutic agents.

Most NP carriers use either passive absorption or receptor-mediated transcytosis to cross the BBB. Framing of purpose, ie. peptide or peptidomimetic monoclonal antibody, i.e. recognized by BBB endothelial receptors, is the most common strategy to bypass the BBB. As a result, AuNPs have become an alternative delivery vehicle to the CNS due to their small size and surface properties. Several endogenous BBB receptors have been used as targets for modified ligands such as transferrin (Tf), insulin, glutathione, and low-density lipoprotein (LDL).

An important clinical opportunity for AuNPs is to deliver drugs to glioblastoma multiforme (GBM), the only fatal primary brain tumor. GBMs are also the most common primary brain tumor in adults, with approximately 12,000 new diagnoses in the United States each year. GBMs are difficult to treat tumors with a five-year survival rate of less than 5%, even with aggressive therapy, including surgery, chemotherapy, and radiation therapy. Surgical resection to remove the tumor is the main treatment. In most cases, curative resection is not possible because the tumor invades the normal brain parenchyma. Standard of care (SOC) systemic therapy increases survival by only months compared to no therapy. In contrast, Au NPs below 8 nm in diameter were successfully targeted to the GBM via receptor ligands. For example, Tf-coated Au NPs have been shown to specifically target tumor cells. A multifunctional Tf-coated Au NP that encapsulates hydrophobic drugs with a non-covalent bond is preferred. The non-covalent bond does not require a change in FDA-approved dosage forms and the drug remains in the active formulation. Non-covalent drug binding also facilitates drug loading and unloading compared to previously used covalent bonds or drug modifications.[27]

Cancer of the digestive tract

Since, one of the main functions of the liver is to filter chemicals from the bloodstream, it seems at first glance that liver cancer would be an ideal candidate for Au NPs, but the use of Au NPs for the treatment of liver cancer and spleen cancer, respectively. , presents a special challenge. The challenge is to design targeted Au NPs that are not captured by one of the many blood filtering mechanisms of the liver. Targeted Au NPs, which are filtered by the liver, do not localize to the tumor site and negate the advantage of using targeted nanoparticles in cancer therapy. In Yan's review of approaches for active targeting of nanoparticles to hepatocellular carcinoma (HCC), they narrowed down the best candidates for active and specific targeting of transferrin receptor, EGFR, CD44, and integrin to HCC. Although these candidates are a good starting point, few studies to date have simultaneously demonstrated the ability of Au NPs to bypass hepatocytes and specifically target liver tumor cells.[28]

Lung cancer

Lung cancer is the most common cancer and the most common cause of death in men and women worldwide. Lung cancer is heterogeneous in nature and diagnosis is often advanced, as it develops silently in the lungs and is often associated with high mortality. Colloidal gold has been used to color glass since ancient times. The optical properties of gold and the quantum size of gold NPs (AuNPs) were first reported by Michael Faraday in 1857. In the years since their initial research, interest in the use of AuNPs in nanotechnology has grown tremendously. AuNPs have a size range of 3–200 nm and exhibit excellent optical and electronic properties as well as stability and thermal properties. Depending on the application of AuNPs, they have been prepared in various shapes and sizes, including gold nanospheres, nanocages, nanostars, nanoshells, and nanoshells. AuNPs are particularly useful in drug discovery because they have several properties that make them good candidates for drug delivery applications.

First, AuNPs are non-toxic, inert and compatible in biological systems and easy to synthesize. Colloidal gold is particularly useful in cancer therapy because AuNPs can be targeted to tumor tissue and using Surface Enhanced Raman spectroscopy as a detection method. There are many reports on the use of AuNPs as probes for the detection of certain blood cancers and cancer biomarkers in nanomedicine. AuNPs were a part of studies in lots of regions including in vitro assays and tissue imaging. Other approaches include thermal ablation-mediated AuNPs and radiotherapy treatment enhancement. In the gold study, the nanospheres were labeled with a Raman reporter and a thin layer of thiolated PEG. AuNPs can also be coated with cancer drugs. The chemotherapeutic cancer drug methotrexate (MTX), a dihydrofolate reductase inhibitor, can be conjugated to AuNPs (MTX-AuNP). An in vivo mouse study shows that MTX-AuNPs reduced tumor growth in a Lewis lung cancer model, while free MTX had no effect. Also, AuNPs were coated with TLR4 ligand and were shown to downregulate TLR4 expression in A549 cells, suggesting that this type of NPs can be used as an adjunctive therapy. Previous studies show the use of different types of inorganic nanoparticles in cancer diagnosis, as the role of AuNPs in connection with CT imaging is promising. In addition, the use of AuNPs as biosensors can differentiate and determine the histological diagnosis of different types of lung cancer.

The sensor profiles volatile organic compounds (VOCs) in lung cancer cells using AuNP sensors and gas chromatography-mass spectrometry analysis. The AuNP sensor was able to differentiate the VOC profile between healthy and cancer cells, SCLC and NSCLC, and NSCLC cell subtypes. Interest in exhaled breath analysis to diagnose diseases such as cancer is long-standing. Breath analysis has many advantages in the clinic, including being safe, feasible, readily available, and noninvasive. In addition, the breath sample is less complex compared to blood plasma/serum or urine. An AuNP biosensor was developed to detect lung cancer from human exhaled breath. The biosensor uses a combined approach with multiple AuNP-based chemiresistors and pattern recognition assays to distinguish lung cancer patient breath from a healthy control patient.[29]

Liver cancer

Liver cancer is the most common cause of death in the world. The mortality rate of this cancer is very high and approximately all patients die within a year. Most liver cancers are diagnosed at an advanced stage where an invasive approach is the only treatment with a survival rate of 10-30%. Despite significant advances in its treatment (surgery, chemotherapy, and radiation therapy), eradication of cancer cells is still limited and survival rates have not significantly improved. Therefore, new screening, diagnostic and treatment methods seem necessary. Cancer nanotechnology has emerged as a new field of medicine aiming to achieve breakthroughs in both cancer diagnosis and therapy. Today, nanotechnology has had a major impact on the development of more effective diagnostic and therapeutic methods. Due to their unique physicochemical and biological properties, new metal nanoparticles have attracted great interest in the field of nano-oncology. For example, nanoscale gold spheres are red or purple, and silver metal nanoparticles are yellow in aqueous solution. They have a strong UV-visible excitation band not visible in the spectrum of bulk metals and unique and highly tunable optical properties known as localized surface plasmon resonance (LSPR). Due to the high surface-to-volume ratio of nanoparticles, their plasmon intensity is very sensitive to size, shape, and dielectric properties. These properties allow them to be applied in the development of new biosensors and chemical sensors. Several metal nanoparticles have strong magnetic properties, prompting researchers to use them in many fields, including biomedicine, magnetic fluids, magnetic resonance imaging (MRI) data storage, and environmental remediation.

Most applications of GNPs in nanomedicine are based on an optical phenomenon known as localized surface plasmon resonance (LSPR). When a metal particle is exposed to electromagnetic waves of a certain wavelength, the insulator can induce a synchronized oscillation in the conduction band electrons called surface plasmon resonance (SPR). A typical metal for defining SPR groups is gold. According to the Mie theory, the position of the LSPR band of GNPs depends on the particle size, shape, structure, composition and dielectric constant of the surrounding medium. By varying these factors, GNPs can achieve tunable absorption in both the visible and near-infrared (NIR) regions. As the LSPR band shifts to the near-infrared (NIR) range of 700-900 nm, the so-called transparent window, light can penetrate deep into soft tissues, making them suitable for in vivo medical applications such as screening, diagnosis, and cancer cell therapy.[30]

Bladder cancer

Bladder cancer (BC) is the fourth most common cancer in men and the tenth most common cancer in women. As the overall prognosis of BC has not changed over the past 30 years, there is an urgent medical need to develop new diagnostic and therapeutic approaches. GNPs have long been used to diagnose and treat many types of tumors. Its properties, such as high surface-to-volume ratio, stability and easy synthesis, as well as its non-toxicity, have led to its use as a nanocarrier for many drugs and also enabled the accumulation of therapeutic agents in the tumor environment. . GNPs play a very important role as drug carriers due to their low toxicity, compatibility with patient cells, surface plasmon resonance (SPR), optical and tunable properties. They can be made into a wide area core with a diameter of 1-150 nm, which makes it easy to control their propagation. In addition, the negative charge caused by MNP makes them easily convertible. This means that they can be designed simply by decorating different biomolecules, drugs, targeting ligands and even genes. GNP extract showed antifungal properties with high cytotoxicity and negligible concentration in BC and prostate cancer cells. Dichloromethane and hexane fractions obtained from GNPs showed high antibacterial and antifungal activity and cytotoxicity in T24 and PC-3 cells studied [142]. Xing et al. a recent study investigated that new chemotherapeutic GNPs were equipped to treat BC [143]. MNP was produced with Citrus aurantifulia seed extract as the limiting factor. Several important tools such as Fourier transform infrared (FT-IR), transmission electron microscopy (TEM), UV-Vis, energy dispersive X-ray spectroscopy (EDS) and field emission scanning electron microscopy have been used to characterize GNPs. (FE-SEM). In UV-Vis, a clear peak at 522 nm indicated the formation of MNP. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay was performed for BC in several cell lines including (HT-1376, grade 3 carcinoma), TCCSUP (grade). IV , transitional mobileular carcinoma, SCaBER (squamous mobileular carcinoma) and UM-UC-3 (transitional mobileular carcinoma). GNPs showed very low cell viability and dose antiBC properties against HT-1376, TCCSUP, SCaBER and UM-UC-3 cell lines. An excellent result of the anti-BC properties of GNPs was obtained for the SCaBER cell line. In addition, these GNPs were suitable suppressors of cholinesterase and α-glucosidase enzymes. If these results are confirmed in clinical trials, GNP may be used as an antioxidant, antidiabetic, anticholinergic and anti-BC dietary supplement in humans.[32]

Breast cancer

Gold nanoparticles show promise in both breast cancer imaging and therapy. From a logistical point of view, most breast tumors occur relatively close to the skin surface, where they are easily accessible and treatable despite the limited tissue penetration of the

NIR laser. Intratumoral injection may also be useful for some superficial tumors, as some studies have shown that only 0.7-5% of an intravenously injected gold nanoparticle dose accumulates in the tumor tissue. Nanoparticle delivery may thus be useful not only for imaging or treating early stage disease, but also for palliative local therapy of advanced breast tumors.

From an imaging perspective, the contrast provided by gold (an element with a higher atomic number than calcium) would be even stronger in mammography. In addition, intraoperative imaging of surgical resection margins based on tumor-specific nanoparticle uptake and non-contact high-field gold nanoparticle imaging techniques can help surgeons ensure resection margin. The challenge is to find an ideal method to focus gold nanoparticles on tumor cells and not on benign breast tissue.

Therapeutically, there is always a need for minimally invasive techniques to treat breast cancer, especially to preserve cosmesis in the treated breast and to minimize the risk of lymphedema associated with axillary lymph node dissection. Although hyperthermia therapy is still considered experimental and requires significantly more research before its widespread clinical use, hyperthermia using ornanoparticles may prove useful in the future. Noninvasive imaging with gold nanoparticles can also help decide whether to forego axillary lymph node dissection in special cases involving positive sentinel lymph nodes, which has not yet been widely accepted.

Gold nanoparticles may also be useful in overcoming challenges inherent in current breast cancer treatments. Potential advantages include increasing the radiation dose for recurrent tumors in a previously irradiated field or radiation sensitization similar to hyperthermic therapy of recurrent tumors. The combination of hyperthermia and photoelectric dose escalation of radiation therapy can be effective in the treatment of superficial inflammatory breast cancer or post-mastectomy chest wall recurrence. Sensitizing tumors to conventional therapies by targeting chemotherapy, oligonucleotides or biologics using the EPR effect and tumor-specific targeting strategies can also overcome the challenge of treating triple-negative cancers by targeting other cell surface receptors that may not be proliferation and proliferation factors. survival, but still sufficiently overexpressed to allow docking of conjugated nanoparticles.[35]

Oral cancer

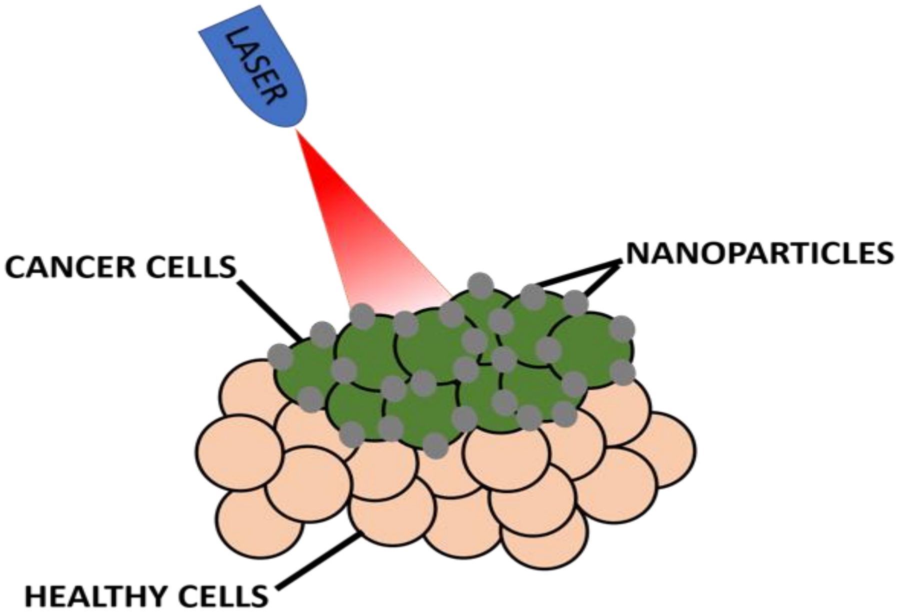
Oral squamous cell carcinoma (OSCC) is a common and aggressive cancer that invades surrounding tissues, metastasizes, and has a high mortality rate. Conventional treatment strategies have improved significantly over the past two decades, but the prognosis remains poor. A major challenge for oncologists in the treatment of OSCC is the complex anatomy of the head and neck, which limits surgical access to tumors. In addition, surgical removal of these tumors is associated with tissue deformities and poor quality of life. Traditional chemoradiotherapy appears as an aid in the treatment of oral cancer to overcome surgical impossibility. However, their side effects are quite debilitating, such as severe oral mucositis, dysphagia and osteomyelitis. Over the last two decades, gold nanoparticles (AuNPs) have been used as innovative tools to improve cancer diagnosis, imaging and therapy. Several reports have introduced approaches to conjugate various ligands to AuNPs due to their simple synthesis and easy surface manipulation, which improves active tumor targeting in vitro and in vivo. Dreaden et al. showed that tamoxifen AuNPs selectively target estrogen receptor alpha in human breast cancer cells in vitro.

In addition, Huang et al. reported that IgG-AuNPs could selectively target human epidermal growth factor receptor-expressing oral squamous cell (HSC-3) cells. Our group previously showed that chemically modified AuNPs using the cancer cell membrane-targeting peptide arginine-glycine-aspartic acid (RGD) enhanced selectivity and uptake by cancer cells through receptor-mediated endocytosis. In addition, we conjugated a novel Wnt/B-catenin pathway inhibitor (XAV939) to AuNPs to interact with and target cancer cells in vitro. Cytotoxicity and uptake data show that the efficacy of XAV939 was significantly increased when presented as bioconjugates of AuNPs compared to its free form.[34]

GOLD NANOPARTICLES IN DIFFERENT ANTI-CANCER THERAPY

1. Photothermal therapy

Due to their unique properties, such as absorption and scattering of electromagnetic radiation, gold nanoparticles are of particular interest for use in photothermal therapy (PTT). This treatment strategy involves using electromagnetic radiation to generate heat to thermally kill cancer cells. Exposure to heat, both in the form of local heating and whole-body hyperthermia, has been used in tumor treatment since the 19th century. Local and general hyperthermia causes cell membrane disruption and protein denaturation, ultimately leading to cell death. Unfortunately, healthy tissues are also damaged during this process, which is the main disadvantage of PTT and greatly complicates its clinical use. This disadvantage has been partially overcome by the use of laser radiation, which allows controlled and precise destruction of cancerous tissue. Modern PTT methods are characterized by improved specificity, minimal invasiveness, and precise spatiotemporal selectivity, and represent a promising alternative in the treatment of chemotherapy-resistant cancers.[40]



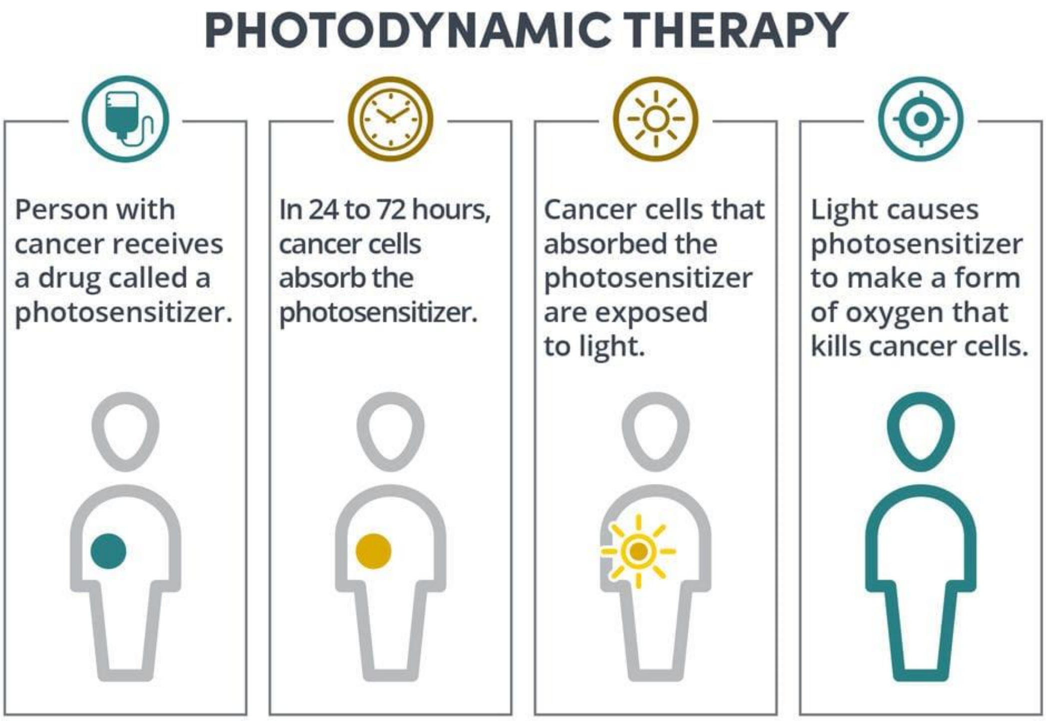
The use of gold nanoparticles in PTT is determined by their size, shape and structure, which greatly influence the photothermal properties. To this end, gold nanorods can be a valuable tool for modern PPT, as their length and width can be manipulated, which not only affects the absorption and scattering band from the visible to the NIR region, but also improves their absorption and scattering. cross sections A similar effect can be achieved by varying the relative size of the gold nanoshell thickness and core radius. This enables the development of AuNRs and AuNSs with specific properties adapted to the location and size of the tumor. In addition, aggregation of nanoparticles has been shown to significantly affect their optical and thermal properties. For example, while different types of AuNS can be inefficient in the near-infrared region, their aggregates can be very efficient at remarkably small interatomic distances (less than 10% of their diameter). It has been demonstrated that such clusters can form both inside the cell and on its surface, which must be taken into account when designing PTT experiments.[41]

2.Radiotherapy

Radiation therapy is one of the most common methods in cancer treatment. It is based on the use of high-energy radiation to destroy tumor cells. Radiosensitizers can effectively increase the radiation dose at the cellular level and thus improve the effect of radiotherapy. GNs can act as an excellent radiation sensitizer in radiotherapy. This is because GNs accelerate DNA strand breaks when exposed to gamma or X-rays. To effectively use GNs in radiotherapy, it is important to determine which size has the best therapeutic effect. Liang et al. performed a detailed study on the effect of radiation therapy on GNs of different sizes. Their group performed radiosensitization studies in vitro and in vivo with 4.8, 12.1, 27.3 and 46.6 nm PEG-coated GNs. Compared with 4.8 and 46.6 nm particles, 12.1 and 27.3 nm GNs were more widely distributed into cells and had better therapeutic effects, causing almost complete tumor disappearance. These experimental results can help to choose a more appropriate GN size to improve radiotherapy.[43] Although GNs have obvious advantages as radiosensitizers, there are a number of problems that prevent their use in radiotherapy. A common problem is how to achieve selective targeting and rapid removal of GNs to reduce radiation dose and healthy tissue exposure. An ideal radiosensitizer has improved tumor retention and plays an important role in improving tumor radiotherapy. Liang et al. reported that GSH-capped ultrasmall gold nanoclusters (2 nm) served as a metabolizable radiosensitizer for highly effective cancer radiotherapy. Thanks to the extremely small hydrodynamic diameter and biocompatible surface,
The therapeutic principle of radiation therapy is to damage intracellular DNA by direct or indirect exposure to external x-rays or y-rays. Therefore, the effectiveness of radiation therapy is limited by insufficient DNA damage and rapid DNA repair during and after therapy. This question has long been the focus of translational radiotherapy research.[45]

3.Photodynamic therapy

Photodynamic therapy (PDT) is a clinically approved cancer treatment that uses non-toxic dyes and harmless visible light in combination with oxygen to generate high levels of ROS to kill cells. The hydrophobic nature of most photosensitizers renders them insoluble under physiological conditions and hinders their systemic administration. In addition, the non-specific distribution of photosensitizers in the body can cause serious side effects when patients are exposed to sunlight. GNs can transport drugs providing higher stability and specific uptake into tumors, and thus have been widely used to deliver photosensitizers in photodynamic therapy of cancer. In addition, the combination of metal nanoparticles and photosensitizer can increase the production of 1O2 compared to a free photosensitizer. Burda et al. used a PEGylated ornanoparticle (5 nm) to deliver hydrophobic drugs for PDT in a mouse model. This administration method significantly shortened the drug administration time and improved drug transport to the tumor. Burda et al. investigated the mechanism and pharmacokinetics of drug delivery in a system containing non-covalent conjugates of PDT anticancer drug with GNs (5 nm). This study demonstrated that hydrophobic drug delivery to mouse tumors by passive accumulation of GNs



achieved rapid release and deep penetration into tumor tissue. Burda et al. covalently linked the photoprecursor Pc 227 with GN (5.5 nm) to form the photodynamic therapeutic drug Pc4 under 660 nm laser irradiation. This facilitated controlled drug release, which could maximize drug accumulation in the target tissue.[46] Broome et al. achieved targeted therapy by constructing GNs (5 nm) conjugated with epidermal growth factor (EGF) peptide and PDT drug. The results showed that the intracellular uptake of GNs by EGF peptide increased the intracellular accumulation and therapeutic efficacy of Pc 4.[47]

APPLICATION OF AuNPs IN CANCER MANAGEMENT

1.AuNPs as drug delivery agents targeting cancer cells

AuNPs as drug carriers can improve drug pharmacokinetics, thereby reducing nonspecific side effects and achieving targeted drug delivery of higher doses. An important application of AuNPs is their use as transport vehicles to transport molecules into cells. The payload can be a small molecule drug or a large biomolecule such as protein, DNA or RNA. However, several factors must be considered when designing an effective drug delivery system. Properties of AuNPs, such as size, charge, and surface chemistry, have been shown to influence their uptake and subsequent intracellular fate.[50]

Gold nanoconjugated cetuximab and gemcitabine were shown to highly target pancreatic cancer cells with high epidermal growth factor receptor (EGFR) expression. Chen et al used approximately 14 nm AuNPs as a methotrexate (MTX)-binding carrier to study side effects in vitro and anticancer effects in vivo. The results showed that compared to MTX alone, MTX bound to AuNPs can be rapidly and efficiently concentrated in tumor cells, which significantly reduces the dose-dependent effect of efficacy. Goel et al also conducted a similar study and found that AuNPs can deliver specific infrared photothermal damage to tumor cells in addition to drugs that can be combined with near-infrared radiation.[51]

2.Application of AuNP in tumor imaging

The most effective way to improve the prognosis of tumors is early diagnosis. Precisely, intensity-modulated radiation therapy such as 3-dimensional conformal radiation therapy and image-guided radiation therapy, accurate and clear images are important in delineating tumor target areas. In recent years, many studies have attempted to use functional imaging to develop tumor radiotherapy plans. Although single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have greater sensitivity and specificity in distinguishing tumors from normal tissues, their spatial resolution is poor. High spatial resolution is important to improve tumor treatment ratio. Commonly used contrast agents are iodine-containing agents that have a short half-life in the blood (less than 10 min) and are less tumor specific. With the rapid development of nanotechnology, the application of multifunctional nanoparticles such as iron oxide nanoparticles, carbon nanoparticles, GNPs, etc. in medical imaging has become important. Among these nanoparticles, AuNPs have attracted increasing attention due to their mature synthesis, stability, and especially high X-ray absorption.[52]

AuNPs are characterized by small size, good biocompatibility, and high atomic number, which means that AuNPs are potentially good contrast agents. Currently, AuNPs target tumor cells in two ways: passive or active. Passive targeting uses only the osmotic stress effect (EPR) to approach the tumor tissue and produce enhanced imaging. Active targeting is the coupling of AuNPs with tumor-specific targeting agents such as EGFR monoclonal antibodies to achieve active targeting of tumor cells by GNPs. When the energy exceeds 80 keV, the mass saturation of gold is greater than that of iodine, suggesting that a gold dwarf is more favorable in evolution. Rand et al used mixed AuNPs with liver cancer cells and X-ray imaging and found that gold-nano mixed liver cancer cells were significantly more effective than plain liver cancer cells. With this new technique, tumors with a diameter of a few millimeters can be detected in life, which is very important for early diagnosis.[53]

Application of AuNP for tumor radiosensitization

The tissue distribution of AuNPs depends on its own parameters, such as size and ability to inactivate tumor cells. Radiation therapy is widely used for almost all types of tumors, such as breast cancer. The rays include X-rays, gamma rays and high-energy particles. However, radiation therapy cannot distinguish cancerous tissue from normal tissue. Therefore, reduction of normal tissue damage remains a limiting factor in radiotherapy. Herold et al injected 1.9 nm AuNPs into breast cancer model mice and found that tumor volume was dramatically reduced and 1-year survival was higher after 2 min of irradiation (30 Gy). Stern et al injected AuNPs into the tumor site with radiotherapy and found that the tumor volume was significantly smaller and did not increase significantly over time.

Targeting AuNPs is a hot area of current research. By combining chemical drugs or some biomacromolecules with AuNPs through chemical methods, it can play a role in reducing toxicity and increasing efficacy by changing the volume, mass and charge of AuNPs. Currently, there is no clear conclusion about the radiosensitization mechanism of AuNPs. AuNPs under hypoxic, normoxic, and aerobic conditions and irradiated them. The uptake of AuNPs by cells under hypoxic conditions was higher than under aerobic conditions. In hypoxic conditions, the proliferation of breast cancer cells is also significantly reduced. AuNPs showed a better sensing effect under normoxia and moderate hypoxia. However, no significant sensitization occurs under hypoxic conditions. Yasui et al concluded that AuNPs accumulate mainly in the cytoplasm and increase the expression of endoplasmic reticulum stress-related proteins, reducing DNA repair, inhibiting the expression of DNA repair-related proteins, and promoting apoptosis.[54]

4.AuNP application in tumor hyperthermia

The thermotherapy mechanism involves the initiation of heat stress in cells at a temperature of 42-470 C, which leads to cell activation and/or initiation of intracellular and extracellular lysis mechanisms. The effects of hyperthermia on intracellular and extracellular processes include changes in signal transduction, induction of apoptosis, reduction of perfusion and tumor oxygenation, etc. AuNRs or AuNSs have notable advantages in absorbing and scattering near-infrared light (wavelengths 650-900 nm). When exposed to electromagnetic radiation, especially near-infrared light, AuNPs can generate heat through surface plasmon resonance effects. Since the absorption peak of AuNPs is in the visible range (450-600 nm), the absorption of near-infrared light in normal tissues is very low. Stimulation of AuNPs with infrared laser radiation induces hyperthermia and minimal damage to normal tissues. Therefore, gold-nano-mediated thermotherapies have the advantage of specificity and less trauma compared to traditional methods. In a mouse model of colon cancer, the researchers injected mice with PEG-conjugated AuNPs, and the AuNPs were deposited at the tumor site and irradiated with infrared light at 800 nm. This treatment significantly prolonged the survival of the mice. In addition, the skin reaction in the normal part of the body did not differ from the location of the tumor.[55]

AuNPs absorb near-infrared radiation, which accelerates the increase in tumor temperature, and can also be used to improve X-ray absorption. The combination of hyperthermia and radiation therapy is synergistic. When the tumor was heated by x-rays to 43.50 C for 2 hours, the heat addition ratio is 8:1, making hyperthermia one of the most effective radiosensitizers. However, tumor hyperthermia has some limitations, such as poor specificity, difficulty reaching deep tumors, and heat tolerance at an early stage.[56]

5.AuNP application in tumor gene therapy

Gene therapy is a new form of treatment that began in the late 20th century and offers an ideal way to treat cancer. Targeted delivery of nucleic acids to tumor cells is a key process in gene therapy. Effective transfection reagents must protect nucleic acids from degradation by nucleases, and nucleic acids are released from cells and function in the nucleus in activated and released forms. AuNPs protect the DNA surface from DNase I degradation. On the other hand, due to steric hindrance, the enzyme cannot bind to the DNA on the surface of the particles and the enzyme did not degrade it. On the other hand, the highly concentrated concentration of ions around the DNA prevents the enzyme from working. AuNPs have a large specific surface area and are easy to modify. They can be used as an ideal transfection reagent, loading large amounts of nucleic acid while controlling surface charge and improving water loss, improving transfection efficiency and reducing toxicity.[57]

CONCLUSION

The role of gold nanoparticles (PNB) in cancer therapy is a promising frontier against cancer. Their versatile properties, including tunable size, shape and surface properties, have paved the way for innovative approaches in cancer therapy. From improving drug delivery to precise tumor destruction through photothermal therapy, GNPs have shown significant potential.

In addition, their contribution in diagnostic imaging and their synergistic effect in combination therapy offer comprehensive strategies for early detection, targeted treatment and improved treatment outcomes. However, there are still challenges in optimizing their biocompatibility and ensuring long-term safety.

Despite these obstacles, the continued progress of MNP-based therapies is promising. Further research focused on refining these properties, improving biocompatibility and addressing safety aspects will be crucial for the successful transfer of these innovations from laboratories to clinical applications. The evolving landscape of gold nanoparticles in cancer therapy is a sign of hope, offering individualized, effective and minimally invasive therapies that could significantly impact cancer care in the future.

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