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Mini-review

Gold nanoparticles in breast cancer treatment: Promise and potential pitfalls

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ABSTRACT

Despite remarkable achievements in the treatment of breast cancer, some obstacles still remain. Gold nanoparticles may prove valuable in addressing these problems owing to their unique characteristics, including their enhanced permeability and retention in tumor tissue, their light absorbance and surface plasmon resonance in near-infrared light, their interaction with radiation to generate secondary electrons, and their ability to be conjugated with drugs or other agents. Herein, we discuss some basic concepts of gold nanoparticles, and early results from studies regarding their use in breast cancer, including toxicity and side effects. We also discuss these particles' potential clinical applications.

1. Introduction

Intensive screening and advanced treatment modalities have reduced the incidence of breast cancer and the rate of breast cancer–related mortality [1,2]. A relatively new concept of breast cancer as a "chronic disease" reflects not only increased survival rates but also the importance of patients' quality of life. Courtesy of gene expression profiling having prognostic or predictive significance personalized therapy enables tailored treatment avoiding chemotherapy in subgroups unlikely to have much benefit. In addition, minimally invasive approaches to treating early-stage breast cancer now consider the patient's cosmetic appearance and minimize the lifelong sequelae of lymphedema. However, many challenges in treating breast cancer patients remain, including reducing treatment-related adverse events, managing triple-negative breast cancer despite poor outcomes and the lack of a therapeutic target, and balancing treatment toxicity with quality of life in patients with metastatic cancer who have already received extensive therapy.

To overcome these obstacles, researchers have introduced the use of nanotechnology in breast cancer diagnosis and treatment [3]. In this context, nanotechnology involves the use of nanoparticles that are small bits of matter of about 1–100 nm in two or three dimensions, according to the American Society for Testing and Materials. Matter on the nanoscale often offers unique properties not seen in bulk matter or in solutions, and their interaction with body tissues differs from that of drugs or transplants. Several technological advances now make it possible to design and characterize nanoparticles by using a large variety of organic and inorganic materials to obtain the desired properties. The research literature on cancer nanotechnology has exploded over the last decade. Our focus here is on one of the more promising variants for the treatment of breast cancer—gold nanoparticles. In this review, we summarize the characteristics of gold nanoparticles, their contributions to tumor destruction, their toxicity, and their potential in breast cancer treatment.

2. Characteristics of gold nanoparticles

2.1. Physical attributes

Gold nanoparticles can vary in size, shape, and structure (Fig. 1), and researchers have developed diverse formulations of gold

Abbreviations: AuNPs, gold nanoparticles; AuNSs, gold nanoshells; AuNRs, gold nanorods; CTAB, cetyltrimethylammonium bromide; EPR, enhanced permeability and retention; RES, reticuloendothelial system; PEG, polyethylene glycol; NIR, near-infrared; TEM, transmission electron microscopy; rhTNF, recombinant human tumor necrosis factor alpha; kV, kilovoltage; MV, megavoltage; HER-2, human epidermal growth factor receptor 2; siRNA, small interfering RNA; HAuNSs, hollow gold nanoshells; kVp, peak kilovoltage; LHRH, luteinizing hormone releasing hormone; PAR-1, protease-activated receptor-1; TPIP, two-photon-induced photoluminescence.

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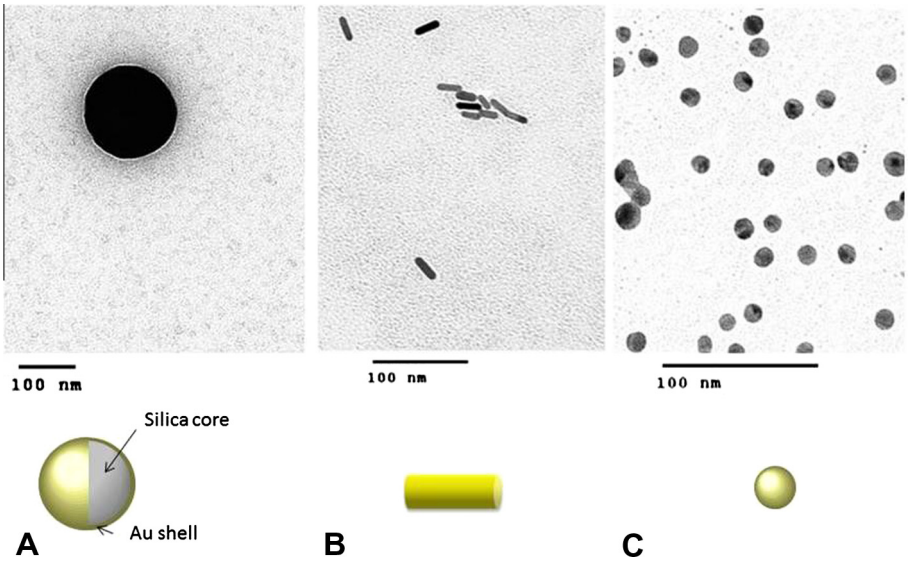

Fig. 1. Some types of gold nanoparticles of interest for breast cancer research. (A) Gold nanoshells usually have a silica core coated with a thin layer of gold. Hollow gold nanoshells can also be made. (B) Gold nanorods are cylindrical, solid gold nanoparticles. (C) Solid gold nanoparticles are spherical nanoparticles comprising gold alone.

nanoparticles for different treatment purposes. Gold nanospheres (AuNPs), which are produced by the reduction of chloroauric acid, are solid balls of gold that range in diameter from only a few to more than 100 nm and are useful for imaging and radiation dose enhancement. Gold nanoshells (AuNSs) are spherical structures comprising a silica core and thin layer of gold, 50–150 nm in size. Their optical properties can be tuned by modifying the core diameter and shell thickness. Gold nanorods (AuNRs) are synthesized from chloroauric acid with a gold seed and a stabilizing agent, usually cetyltrimethylammonium bromide (CTAB) [4]. The absorption wavelength of AuNRs has two peaks depending on the orientation of the particle to an incident beam of light. Size of AuNRs is typically 25–45 nm in longest dimension, and manipulating these plasmonic particles' length-to-diameter ratio (i.e., aspect ratio) changes their peak absorbance wavelength. Depending on their surface charge and functional groups, AuNRs can have higher cellular uptake [5,6]. Nanocages and hollow gold nanospheres are other forms of gold nanoparticles that have excellent plasmonic photothermal activities. Depending on the nature of preclinical or eventual clinical application, these differences in size, shape and surface properties of gold nanoparticles are exploited by researchers for specific cancer therapy scenarios. In addition to presence of an inorganic metallic substrate, this tunability to create spheres, shells, rods, and cages of varying sizes and shapes distinguishes gold nanoparticles from other commonly used non-metallic nanoparticles such as liposomes and polymers.

2.2. Passive and targeted accumulation in tumors

Gold nanoparticles can easily permeate tumor vasculature and remain in tumors owing to the enhanced permeability and retention (EPR) effect, as gaps in tumor vasculature, whose sizes range from 100 nm to 2 μm, are larger than the gaps in the endothelial lining of normal capillaries. Gold nanoparticles easily pass through these gaps and, because tumors lack lymphatic clearance and have a disordered extracellular matrix, are able to remain in the tumor tissue. However, the tumor uptake of gold nanoparticles *in vivo* is significantly lessened by the opsonization of the nanoparticles with plasma proteins and their subsequent phagocytosis by reticuloendothelial system (RES) components such as monocytes and macrophages. Thus, most injected gold nanoparticles are eventually sequestered in the liver and spleen. Coating the nanoparticles with the polymer polyethylene glycol (PEG) [7] acts like a "stealth" cloak, preventing the uptake of nanoparticles by the RES, thus prolonging their circulation time and increasing their concentration in tumor tissue.

Gold nanoparticles can accumulate in tumor across the blood–brain barrier in brain tumor models, as contrasted with normal brain tissue [8]. Furthermore, conjugated gold nanoparticles can be delivered into brain parenchyma using a carrier-mediated influx of endothelial cells [9]. Such mechanisms can be used to carry drugs to specific targets within the central nervous system. In larger tumors, hypovascular cores confine the neovasculature's leakage of gold nanoparticles to the periphery of the tumor; gold nanoparticle-loaded macrophages and T cells can be used to overcome the difficulties of treating the hypovascular area.

2.3. Hyperthermic effect

Gold nanoparticles such as AuNRs or AuNSs have optical properties of light absorbance and scattering in near-infrared (NIR) wavelengths (650–900 nm) [10]. With exposure to electromagnetic radiation, especially an NIR laser, gold nanoparticles can generate heat via the surface plasmon resonance effect (Fig. 2). Because its peak absorbance wavelength is in the visible range (450–600 nm), NIR light is transmitted through normal tissue components with minimal absorption [11,12]. Therefore, gold nanoparticles stimulated with NIR laser illumination can induce hyperthermia [13] in tumor tissue with little damage to normal tissues. In a pivotal study of mice with subcutaneously implanted colon cancer cells, intravenous administration of AuNS-PEG conjugates resulted in the passive accumulation of the AuNSs within the tumors, and subsequent illumination of these tumors with an 808-nm NIR laser successfully ablated the tumors. Compared with mock treatment, this treatment extended the survival of mice. The NIR laser-induced skin reaction in the AuNS-treated mice was no different from that in mice undergoing mock treatment, except that the AuNS-treated mice had a greater skin reaction at the tumor site [14].

2.4. Radiosensitizer properties

Owing to the high atomic number of gold, gold nanoparticles can also be used as imaging contrast agents and radiosensitizers