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GRAPNEL EVICTION OF CANCER WITH GOLD NANOPARTICLES

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ABSTRACT

Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules, by controlling shape and size at a nanometer scale of nanoparticles. At present, there seems to be heightened interest in the application of gold nanoparticles (AUNPs) to the management of cancer, encompassing diagnosis, monitoring and treatment of the disease and they are being investigated as drug carriers, photothermal agents, contrast agents and radiosensitizers. This review highlights the features, synthesis and applications of gold nanoparticles in cancer remedial treatment.

KEYWORDS: Nanotechnology, Gold, Nanoparticles, Cancer, Contrast agents, Photochemical therapy. Radiosensitizer, Photothermal

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INTRODUCTION

Nanotechnology is the one of the most important of therapeutic innovation such as drug delivery with interest also in in vitro diagnostics, novel biomaterial design, bioimaging therapies and active implants[1,2][1,2]. Nanoparticles, according to the Amercican Society for Testing and Materials (ASTM) standard definition, are particles with a length that range from 1 to 100nm in two or three dimensions[1]. Most commonly studied nanoparticles are carbon nanotubes, gold nanoparticles and cadmium selenide quantum dots[3,4] Gold nanoparticles (GNP) are not new to this world, in the 19th century; Michael Faradey[5] published the first scientific paper on GNP synthesis, describing its production. In the late 20th century, techniques' including transmission electron microscopy (TEM) and atomic force microscopy (AFM) enables direct imaging of GNPs and control of properties such as size and surface coating was refined . GNPs are synthesized using physical, chemical and biological methods[6,7]. Various chemical methods used for the synthesis of GNPs, includes (i) sodium citrate mediated reduction described by Turkevich (1951) and Fren (1973); (ii) sodium borohydride mediated reduction method (Brustand Schriffin;1994)[6,7] (iii) Seed mediated growth proposed by Schmid et al (1996)[8]. The most widely used chemical method for synthesis of GNPS is the seed mediated growth. Sastry et al reported the synthesis of GNPs using biological method utilizing three different microbes, namely fungus Fusariumoxysporum, fungus Verticillium sp. and actinomycete Thermomonosporasp and these biological methods have proved to be more ecofriendly, simpler and more reproducible alternative to chemical methods. Experimental studies have shown that use of fungus Helminthosporumsolani, when incubated with an aqeous solution of chloroaurate ions, produced a mixture of extracellular gold nanocrystals in diverse shape and size. These smallest separated gold nanoparticles when conjugated to Doxorubicin (DOX) demonstrated efficient uptake and cytotoxicity in HEK293 cells[9,10,11]. For instance stem extracts of Cassia fistula of Leguminosae family and leaf extracts of tropical almond tree (*Terminalia catappa*), rose plant (*Rosa rugosa*), Mangnolia kobustree and persimmon *(Diopyros kaki*) were used for the synthesis of gold nanoparticles; rose geranium plant *(Pelargonium graveolens*) extract was used to synthesize decahedral and icosehadral shaped gold nanoparticles; lemon grass (*Cymbopogonflexuosus*) extract has been used to synthesize gold nanostructures of various shapes, namely gold nanospheres and gold nanotriangles; neem (*Azadirechtaindica*) extract used to synthesize gold triangles and hexagons, sugar beet pulp was used to synthesize gold nanowires; and Aloe vera plant extract for synthesizing gold nanotriangles. All of these biosynthetic methods were highly reproducible and are relatively non-toxic[12,13,14,15,16,17,18,19,20]. The physiochemical properties of GNPs including surface Plasmon resonance and the ability to bind amine and thiol groups, allowing surface modification and makes it to play a key role in biomedical applications[21].

Scapegoat GNPs Delivery

GNP targeting to specific organelles maximizes the impact on tumor cells. To this end, GNPs are being developed that accumulate in subcelllular compartments where they destroy intrinsic cancer cell functions that are essential for tumor survival. Once in their proper intracellular location GNPs can enhance cancer cell destruction by different means. This includes the confined delivery of anti-cancer agents[22]. Localized subcellular mechanical damage and an improved efficiency of photothermal ablation due to high local GNP concentrations[23,24]]. Such controlled GNP action will not only increase cancer cell killing but also diminish toxic side effects, because it reduces the neccesary amounts of GNPs and drug load. Candidate compounds for nanoparticles-dependent subcellular delivery are doxorubicin[19], platinum based drugs[25]and paclitaxel[26]. These anti-cancer agents interfere with nuclear and mitochondrial functions, respectively[27,28,29,30]and have been used to functionalize GNPs[19,31,32,33,34]. Aside from drugs, GNPs can also deliver oligonucleotides to alter gene expression and splicing[35]. Once accumulated in tumor tissue, GNPs have to overcome multiple obstacles before they can concentrate in the desired cell compartment.(i) cell surface binding, (ii) cellular uptake, (iii) escape from lysosomes/endosomes, (iv) association with the particular subcellular location, such as nuclei or mitochondria. The first three steps are general features that regulate the intracellular destination of all GNPs[36,37,38,39,40]. Positive charges can also improve AuNP transport to the nucleus, because nuclear localization sequences (NLS) of many proteins are enriched for basic amino acids residues[41,42]. Once bound to the cell surface, GNPs enter the cell; in most cases that occur by energy-dependent process, for which endocytosis is the main route[36,43]. Brown et al had shown that the active component of the platinum bases anti-cancer drug oxaliplatin when conjugated to gold nanoparticles provided improved drug delivery. Naked gold nanoparticles were functionalized with a thiolated polyethylene gycol (PEG) monolayer capped with a carboxylate group. A Platinum complex, [Pt(1R-2R-diaminocyclohexane)H_2O_2]2NO_3,was added to the PEG surface to yield a supramolecular complex with around 280 drug molecules per nanoparticle. The platinum tethered gold nnaoparticles were examined for cytotoxicity, drug uptake and localization in the A549 lung epithelial cancer cell line and the colon cancer cell lines HCT116, HCT15, HT29 and RKO. The platinum tethered nanoparticles demonstrated as good as, or significantly better, cytotoxicity than oxaloplatin alone in all the cell lines and also an unusual ability to penetrate the nucleus in the lung cancer cells[25]. Patra et al demonstrated the high intra-tumoral gold concentrations (4500µg/g) with untargeted GNPs. The GNP-cetuximab-gemcitabine nanocomplex was found to be superior to any of the agents alone or in combination both in vitro and in vivo. Low doses of complex gemcitabine led to < 80% tumor growth inhibition in an orthotropic pancreatic cancer model compared with 30% inhibition using the non-conjugated agents in combination[44,45]. GNPs of ultra-small size (2.8nm) conjugated to doxorubicin were found to be upto five fold toxic to B16 melanoma cells than the drug alone[46]. Gold

nanoparticles functionalized with anti-epidermal growth factor receptor antibodies have been found to facilitate photothermal destruction of cancerous cells expressing EGFRs[47] Similarly, the uptake rate of GNPs can be improved via ligand receptor endocytosis. Upon surface modification of GNPs with folic acid, the uptake amount of GNPs in MDAMB- 435s cells,which had sufficient folic acid receptors, was found to be higher[48]. Also water-soluble doxorubicin conjugated GNPs exhibited a significant pH-responsive drug release profile, when they were stabilized by thiolated methoxy polyethylene glycol (MPEGSH) and methyl thiogylcolate(MTG) at an equi-molar ratio[49]. Nuclear homeostasis is often altered in cancer cells, which display changes in nuclear size, shape, envelope, lamina and chromatin organization, nucleolar function or nucleocytoplasmic trafficking[50,51,52,53,54,55,56] and hence, the nuclei represent primary targets for cancer therapy. Various strategies have been employed to target gold nanoparticles to the nucleus. So far, there is no protocol that has been universally successful for different tumor cells, therefore, GNPs were functionalized with NLSs (nuclear localization sequences), cell penetrating peptides, peptide combinations, oligonucleotides or other moieties[37]. Changes in bioenergetics are a hallmark of many tumors, but mitochondria are also key regulators of apoptotic cell death[57,58]. Unlike the nucleus, mitochondria do not contain large pores that provide easy access for GNPs. Both the outer and inner mitochondrial membranes present barriers to GNPs that are destined for the mitochondrial matrix[59].Common effects of GNPs on mitochondria are morphological changes, loss of membrane potential and production of reactive oxygen species. Unlike GNP delivery to nuclei or mitochondria, strategies for endoplasmic reticulum (ER) targeting are less developed. However, given the importance of the ER for many tumor types and links between mitochondria and ER[60], GNPs located in the ER could play a significant role in cancer therapy. Accumulation at the tumor sites in vivo is a prerequisite for subcellular targeting[12,14] and building on in vitro studies; functionalized GNPS were also used for gene delivery[61].

Gold nanoparticles as contrast agents (Cancer Cell Imaging)

GNPs serve as a contrast agent due to its dynamic properties which include small size, biocompatibility, high atomic number and the ability to bind targeting agents,and their mean[62]. GNPs have the potential to improve contrast with structural imaging modalities, with is possible that functionalized GNPs could be effectively employed in vivo molecular imaging for obtaining information on the metabolic activity of cancer cells and expression of molecular markers. Further, GNPs have been shown to cause radio-sensitization at kilo voltage and mega-voltage photon energies[49]. One of the study reported novel DOX conjugated GNPs with the potential to simultaneously enhance computed tomography (CT) imaging contrast and facilitate photothermal cancer therapy while delivering anti-cancer drugs to their target sites[63]. To date, CT has not been used as a molecular imaging modality because iodine cannot be conjugated to molecular proteins[64,65]. Use of monochromatic x-rays at the European Synchrotron Radiation Facility (ESRF) enabled in vivo GNP dose quantification because gold produces characteristic X-ray spectra which are detectable using an ionization chamber. The nanoparticles could be clearly imaged by both CT and MRI because they accumulated in the kidneys and bladder during renal excretion[66].

Photothermal cancer therapy

Photothermal cancer therapy mediated by GNPs is gaining immense attention in the treatment of cancers and recently several researches have demonstrated the potential use of gold nanostructures of various shapes and sizes in thermal ablation of cancer cells[67,68]. Gold nanoparticles specifically targeted to biomarkers on cancer cells allow molecular specific imaging and detection of cancer within the body. In addition to that GNPs have the highly tunable Plasmon resonances, on account of which the GNPs can absorb light and quickly convert the absorbed light energy effectively into localized heat energy and this property can be harnessed to cause thermal ablation of the cancer cells in a process called nanophotothermal lysis or hyperthermic/ phtotothermal cancer therapy[69,70,71]. Gold nanorods are some of the preferred nanostructures for photothermal therapy as they exhibit highly efficient absorption in the Near-Infra Red (NIR) region, which is the optimal optical wavelength for the penetration of deep tissues for cancer treatment[72]. In-vivo studies using gold nanoshells when administrated to mice intravenously followed by NIR resonant radiation resulted in destruction of tumor cells in mice[73]. However, lack of tumor specificity, difficulty in heating of deep rooted tumors to therapeutic temperatures and thermo-tolerance after initial treatment has limited the use of hyperthermia in cancer treatment[74]. Gold nanorods and gold nanoshells that absorbs in NIR range can mediate best tissue penetration as the hemoglobin and water absorption is decreased predominantly in the optical wavelength of around 800nm (biological NIR window). Thus, for in vivo cancer therapy applications, plasmonresonances of nanoparticles have been optically tuned to be in the NIR region for achieving effective hyperthermia of deeper tissues[75,76]

Gold nanoparticles as Radiosensitisers

It has been stated in the literature by researchers that the GNP radiosensitisation increases photoelectric photon absorption by high-Z materials at kilo voltage photon energies. But it has to be kept in mind that , if sensitization occurs by this physical mechanism, the effects would not be predicted to occur at clinically relevant megavoltage energies where Crompton interactions are dominant[77]. It has been observed that greater radiation side effects occur at the interface with high-Z materials owing to greater absorption of photons and deposition of energy in surrounding tissue from photoelectrons, Auger electrons and characteristics X-rays[78]. Thus in terms of therapeutics , if the high-Z material is present at high concentrations in the tumor than in the normal tissue, an improvement in the therapeutic index should be realized.

Gold nanoparticles on clinical trials

The first GNP therapy to have reached early phase clinical trials is CYT-6091, 27nm citrate coated GNPs bound with thiolated PEG and tumor necrosis factor-α (TNF-α) (Aurimmune; Cytimmune Sciences, Rockville, MD), which has the dual effect of increasing tumor targeting and tumor toxicity[79]. TNF-α is a multifunctional cytokine known to be both cytotoxic and immunomodulatery. Previous clinical trials of TNF-α demonstrated dose-limiting toxicities of hypotension and nausea at concentrations of 225μg m^{-2}, which limited more widespread clinical use[80].

CONCLUSION

Many questions need to be answered before GNP complexes enter routine clinical use. The factors that affect GNP pharmacokinetic, bio-distribution and in vivo toxicity need to be clarified. Targeted GNPs need to exit tumor vasculature, cross the tumor interstitium, enter cells and potentially exit lysosomes to be effective in vivo. They must be able to reach hypoxic cells, which lie far from the vasculature, because these cells are known to be both chemoresistant and radioresistent. Long term studies are required to evaluate the toxicity and mutagenic potential of GNP RES uptake, because particles may remain in cells for many months. A standard approach for physicochemical characterization and pre-clinical testing need to be implemented and this process is being aided by the NCL. Rigorous quality assurance needs to ensure minimal batch-to-batch variation, especially when production is scaled up for clinical use. There is huge potential to use nanaoparticles in cancer therapy. With intense global interest in nanotechnology and particularly in nanomedicine, it is likely that many of these questions will be addresses in the near future.

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