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Review Article

A Review on the Applications of Gold Nanoparticles in Treatment of Cancer

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Abstract: In the recent years, applications of nanoparticles in imaging and treatment of cancer has been the issue of many studies. Among different research some have focused on the dose enhancement effect of gold nanoparticles and the therapeutic potential of phytochemical reduced and bound gold nanoparticles in radiation therapy of cancer. The main idea behind the GNP dose enhancement and how to bound with other molecules in some studies is not able to explain the results specially in recent investigation on cell lines and animal models radiation therapy using GNPs. In the present article the results of the available reports and articles were analyzed and compared and the final status of the GNP-RT was discussed.
Keywords: nanoparticles, gold nanoparticles, treatment of cancer, dose enhancement

INTRODUCTION

Nanoparticles can be explained as particles less than 100nm in diameter that are typically smaller than human cells and comparable to large biological molecules such as enzymes, receptors and antibodies [1]. In cancer treatment, they have supplied better piercing ability for substances used for diagnoses and therapy with lower risk compared to customary drugs [2]. Nanoparticles distribution is determined by factors associated with the tumor microvasculature, in addition to factors inherent to nanoparticles itself, such as size, shape and surface large [3]. In treatment of cancer, targeting and localized delivery are the key challenges. In radiotherapy it is important that normal and tumor tissue receive the lowest and highest doses respectively. Unfortunately, ionizing radiation do not discriminate between cancerous and normal cells. Nanoparticles have the potential to have a revolutionary impact on treatment of cancer. By using nanoparticles we can to selectively attack the tumor cells, while saving the normal cells from extreme burdens of drug toxicity [4]. Nanoparticles have several features that are ideal for oncology applications, including preferential accumulation in tumors, low distribution in normal tissue, bio distribution, pharmacokinetics, and clearance [5]. Among different nanoparticles, gold nanoparticles possess unique features: small size, good biocompatibility, low toxicity, simple source chemistry, and easy surface modification. These characterizes make GNPs, very encouraging candidates for biomedical use and numerous biological applications as biosensors and drug delivery vectors for cancer chemotherapy and radiation therapy[6]. In the present review, the applications of GNP in treatment of cancer will be discussed and the results of the related studies will be reviewed.

The object of the current article was to prescribe the current states of gold nanoparticles(GNP) applications in treatment of cancer especially in radiation therapy. The perusals on GNP and its applications in radiotherapy beams were reviewed and the arguments were conversed.

Interaction of X-ray and different radiations with GNPs:

In this part, the GNP interactions on the cellular level, its molecular partners in biochemical reactions for further optimizations and interactions between GNPs and different source of radiations will be discussed.

For all biological applications of nanoparticles, it is important to understand their interactions with the surrounding biological environment in order to predict their biological impact, in particular when designing the nanoparticles for therapeutic purpose. due to the surface-to-volume ratio, the surface of nanomaterial is very reactive. When exposed to biological fluids, the proteins and biomolecules present therein tend to associate with the nanoparticles' surface. This phenomenon is defined as bio molecular corona formation. The bio molecular corona plays a key role in the interaction between nanoparticles and biological

systems, impacting on how these particles interact with biological systems on a cellular and molecular level.

A. Some studies about interaction of X-ray and different radiations with GNPs:

Have faith in that interactions of X-rays and GNP result in the release of photoelectrons from high Z gold atoms as well as production of auger electrons. The range of these electrons is very short proportionate to photons and a pronounced energy is deposited in cells containing GNP or in direct proximity to gold atoms.

Wan, et-al studied on the interaction between GNP and X-ray irradiation in bovine aortic endothelial cells. They used seven different energies(30, 40, 50, 60, 70, 81, and 100kev). They observed that DEF (Dose Enhancement Factor) in the energy of 40kev was maximum with a value of 3.47. This factor obtained at other energy levels followed the same directions the theoretical calculation based on the ratio of the mass energy absorption coefficients of gold and water. They concluded that when the energy was low, dose enhancement factor is high because electron production increased[7].

Jeynes, et-al investigated about the contribution of secondary electron emission to cancer cell radio sensitization and investigated how this parameter is affected by proton energy and a free radical scavenger. They found that in the range of proton energies(1-250 Mev), the ratio of secondary electron is smaller than X-ray, for this reason concluded that DEF in the X-ray energy is more than photon energy[8].

Jeremic et-al compared the DEF-ratio in kilovoltage and megavoltage energies. They found that kilovoltage radiotherapy carries significantly higher dose enhancement factor that is observed with megavoltage irradiations, the latter usually been at the order of 1.1-1.2. They concluded that in higher concentrations of gold, dose enhancement factor is higher than in lower concentrations[9].

Moshi Geso, et-al in their study used GNPs for the enhancement of radiation effects on bovine aortic endothelial cells in superficial X-ray and megavoltage electron radiation therapy beams. They observed that at 1mM concentration of GNP, enhancement of radiation peaked at 25 times for a kilovoltage X-ray beam while it showed lesser extent effects on electron beams [10].

Monte Carlo Modeling of GNP dose enhancement effect:

Jones, et-al studied on the estimation of microscopic dose enhancement factor around gold nanoparticles by Monte Carlo calculations. They used six different photon sources (I-125, Pd-103, Yb-169, Ir-192, 50 Kvp and 6 Mv X-ray) and treating the scored electron spectra as point source within an infinite medium of water, they quantified the radical dose distribution with Monte Carlo-Code NOREC. They observed that by using GNPs, it is possible to select passive or an active tumor targeting which will maximize the radiobiological benefit [11].

Michael, et-al studied on Monte Carlo simulation of dose enhancements and the spatial properties of the secondary electrons production. The GEANT4 Code was used to simulate and calculated the electrons production from a 2,50 and 100nm diameter GNP. They used four different photonsources (25 and 50 Kvp, CO-60, 6 Mv) and GNP is irradiated in water. They observed that when a GNP was present, depending on the beam energy used, secondary electron production was increased by 10-2000 fold compared to an absence of GNP. Calculations demonstrated that in low-energy, the interactions between GNP and radiation is more than high energies such as megavoltage energies. They concluded that the irradiation of GNP at lower photon energies will be more efficient for cell killing [12].

Bahreynitoossi, et-al used a Monte Carlo model to calculated the tissue dose enhancement factor in the gold nanoparticles and gadolinium. MCNPX Monte Carlo code and four different brachy therapy sources (Co-60, Au-198, Ir-192, Yb-169) was used. To study dose enhancement, a spherical soft tissue phantom with 15 cm in radius was simulated. The concentrations of GNP and Gadolinium were 10,20 and 30 mg/ml. they observed that GNP show higher dose enhancement than Gadolinium nanoparticles and have more clinical usefulness as dose enhancer material [12].

Amato, et-al studied on the dose enhancement effect of GNPs DURING x-ray therapies and evaluation of the anti-angiogenic effect on tumor capillary vessels. They used GEANT4 Monte Carlo code and X-ray tube(150 Kev). The results showed that the radial DEF profiles around the vessel are in close relationship with the radial profile of GNP , there for they concluded that GNP is a new and good method for radio sensitization otherwise it has anti-angiogenic and cytotoxic dose enhancement effects [14].

Chow, et-al investigated about the secondary electron production from GNP in three different diameters (2, 50, 100) and with four types of energies (50 and 250 Kev,1 and 4 Mev). They used GEANT4 Monte Carlo and irradiated spherical GNP in water. Results showed when the GNP size and electron beam energy were high, the secondary electrons are increased. Therefore GNPs can have more clinical usefulness as dose enhancer material [15].

Lin, et-al compared the dose enhancement factor between proton, megavoltage and kilovoltage photons in GNPs by using Monte Carlo simulation.

Their results showed that GNPs have the potential to enhance radiation therapy depending on the type of radiation source. They concluded that proton therapy can be enhanced significantly only if the GNPs are in close proximity to the biological target[16].

Berbeco, et-al researched about the dose enhancement factor in tumor blood vessel endothelial cells via megavoltage and X-ray and targeted GNPs. They used the thin slabs of endothelial with 100nm GNP attached within the blood vessel. The Monte Carlo method is used to calculate the dose enhancement factor with different concentrations of GNP. The results showed the major dose enhancement factor for conventional linear accelerator X-ray. They concluded that when there are organs at risk, we can use the GNPs to focus dose to tumor volume [17].

GNP sensitization in different tumor cells:

Hainfeld, et-al treated the mice bearing subcutaneous EMT-6 mammary carcinoma. They treated two group of mice, one of them treated with radiation alone and other treated with radiation and GNPs. They used X-ray (68 Kevp, 42 and 30 Gy) and same size of GNPs (1.9nm) in tow groups. After treatment, median survival for mices that were treated with radiation and GNPs was 86% versus 20% for another group. The results showed that by using GNPs plus radiation, median survival and long-term tumor control are increased[18]. In another study, they treated subcutaneous (SCCV II) leg tumor in mice were irradiated with X-ray alone and X-ray plus GNPs. they used two different energies (68 and 157 Kev). They observed that in 68 Kev energy, radiation dose was more effective than 157 Kev. The results showed that GNP enhance the radiation therapy of radio resistant mouse squamous cell carcinoma[19].

Another animal study was managed in 2008 Change, et-al. They injected melanoma cells (B16F10) to mice. After GNPs injection, mice were irradiated with electron (25 Gy). They observed that GNPs radio sensitized the melanoma cells. In comparison with control group, tumor growth rate was decreased, peptic signals and survival rates were increased [20].

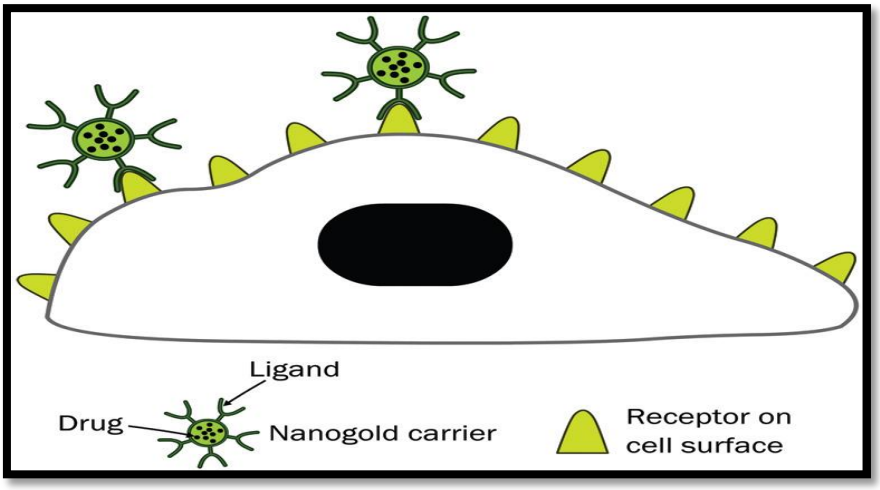
Joh, et-al reported their pilot studies in cell culture research and in an animal model of GBM in which radiotherapy is make perfect by gold nanoparticles. GNPs significantly increased cellular DNA damage in human GBM and resulted in decreased clonogenic survival (DEF=1.3). Finally, the combination of GNP and radiation increased survival of mice with orthotopic GBM tumors. Thuscanbe leveraged to make better the tumor tissue targeting and can be optimized the radio sensitization of tumors by using GNPs[21].

The possible mechanistic effect of GNPs on cell cycle distribution and DNA double-strand break (DSB) repair post irradiation were also studied by Cui, et-al. They found that the presence of GNPs inhibited post irradiation DNA DSB repair due to decreased (RAD57) associated protein expression[22].

Kodiha, et-al studied on nuclear damage in breast cancer cells by using GNP. They wanted to know how GNPs either alone or in combination with mild hyperthermia, altered the physiology of cultured human breast cancer cells. They used the different size of GNPs. After multiple investigations, they concluded that the toxicity GNPs correlated with changes in nuclear organization and function. For this reason, GNPs can be used for cancer killing[23].

Bounded GNPs:

There is significant interest in investigating the therapeutic potential of phytochemical reduced and bound gold nanoparticles (AuNPs) as it bridges the gap between nanotechnology and therapy. In this part, we investigate and discus about some studies.



Fi-1: Schematic diagram showing AuNP carriers conjugated withanticancer drugs and ligands which are recognized by receptors on thesurface of tumor cells [24].

Liu, et-al studied on the enhancement of cell radiation sensitivity by paginated GNPs. To different cells (ENT-6 and CT26) and four different energies (commercial biological irradiator: E=73 Kev, Cu-Ka X-ray source:8.048 Kev, monochromatized synchrotron source:6.5 Kev, linear accelerator 6 MV). They want to investigate about the GNPs effects on EMT-6 and CT26 cell survival rates during irradiation for a dose up to 10Gy. The results showed that after irradiation, in the presence of PEG-GNP, the percentage of surviving cells was decreased. These results could open the way to more effective cancer irradiation therapies by using nanoparticles with optimized surface treatment[25].

Kondet- al studied on the synthesis and characterization of morin reduced gold nanoparticles and flavonoid morin (mAu NPs) and after TEM analysis, they observed that they are readily katen up by MCF-7 cells to induce cell death. They concluded that the cells undergoa transient phase of apoptosis growing for secondary necrosis as the dose and time of mAuNPs treatment increases [26]. In the similar study, Kong et-al studied on the enhancement of radiation cytotoxicity in breast cancer cells by localized attachment of GNP. They studies on breast cancer cell line (MCF-7) versus anonmalignant breast cancer line(MCF-10A) and used Glu-GNPs. TEM results showed that by using Glu-GNPs, significantly cancer killing increased[27].

Song, et-al investigated about the killing effect of GNPs in cancer cells. They want to compared this effect between GNPs alone and Glu-GNPs in Hela and MCF-7 cells. The results showed that lower doses of GNPs and Glu-GNPs enhanced the killing effect using x-rays irradiation, although the apoptotic rate was not altered. They concluded that Glu-GNPs may have a bright future in cancer therapy[28].

This paper reports that thio-glucose bound GNP (Glu-GNP) can be used as a sensitizer to enhance ovarian cancer radiotherapy[29]. The cells were treated by GNP alone, irradiation alone, or GNPs in addition to radiation. The cells treated by Glu-GNPs resulted in an approximate 31% increase in nanoparticle uptake compared to naked GNPs. Compared to the irradiation alone treatment, the intracellular uptake of Glu-GNPs resulted in increased inhibition of cell proliferation. The results showed that the interaction of X-ray radiation with GNPs induced elevated of ROS production, which is one of the mechanisms by which GNPs can enhance radiotherapy on ovarian cancer.

In similar study; they investigated about the effect of GNP type and dosing strategy on in vivo tumor targeting. They examined the in vivo tumor-targeting efficiency of pegylated gold nanoshells (GNSs) and gold nanorods (GNRs) for single and multiple dosing. Mice with a subcutaneous tumor was used to receive intravenous administration for a single and multiple doses of GNS and GNR. Neutron activation analysis showed a significant increase in GNS and GNR accumulation in the liver for higher doses. These results suggest a major effect of particle type and multiple doses on increasing particle accumulation and on tumor targeting ability[29].

Hirsch, et-al demonstration 100nm GNPs maximally accumulated in SK-BR-3 human breast tumors 24hr after intravenous injection. They observed that when a laser tuned to the nanoparticles resonance was applied, average tumor temperature in nanoparticle treated mice was higher than in control mice. The results showed that median survival and tumor growth control in the nanoparticle group are higher than control group[30].

Hong, et-al studied on mechanism of thio-glucose bound GNPs (Glu-GNPs) in the lung adenocarcinoma cell line A549. They observed that radiation and Glu-GNPs could both influence apoptosis. Glu-GNPs reduced A549 cell at the phase S and enhanced those at G2/M. they concluded that Glu-GNPs could induce radio sensitivity enhancement on the lung adenocarcinoma cell line A549 and mechanism may be related to restraining repair of sub-lethal damage, blocking cell at G2/M and inducing apoptosis [31].

CONCLUSION

The idea of using GNPs for radiation therapy has been studied by several experimental and MC simulation investigations during last years. Among NPs, GNP is the most research nanoparticle in cancer therapeutics. In vitro radio sensitization and in vivo tumor growth deceleration attach by longer survival give researchers the proof of using GNPs. Different sizes, density, cell lines, radiation sources and doses have been used at the reviewed studies. Reviewed have demonstration that GNPs can enhance the dose deposition in GNP loaded tumors. Also, more biological experiments on cell lines and animal models are required to clarify the effects of GNPs in treatment of cancer cells.

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