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GOLD NANOPARTICLES IN CANCER TREATEMENT

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Abstract - There has been having rapid development in the field of biomedical applications where nanoparticles can be used for various therapies. The most commonly used nanoparticle for the therapy is Gold nanoparticle which has many unique properties that make it suitable candidate for radio sensitizers. Radiation therapy and chemotherapy can be combined and used for cancer treatment where GNPs are used as anticancer drug carriers. This can be used to as a curative measure and also palliative intent. The major limitation of this tolerated, hence the mechanisms of radio resistance have been extensively studied using Deinococcusradiodurans, the most radio resistant organism ever reported. Yet they are still not translated into clinical use.

Keywords – [Gold nanoparticles, Drug delivery, Radiation dose enhancer, Combined therapy, DNA damage.]

1. INTRODUCTION

Cancer is one of the leading causes of death in the worldwide and patients diagnosed with cancer are expected to reach 22 million in the next two decades. Cancer is diseases where cells grow out of control invade, erode and destroy normal tissues. Cause are due to external factors like chemicals, radiations, viruses and lifestyle, internal factors like hormones, immune conditions, inherited mutations and cellular change. Gold nanoparticles (nanogold) occur as clusters of gold atoms upto 100nm in diameter. Nanogold has unusual visible properties because the particles are small enough to scatter visible light.Advantages of using gold nanoparticles for cancer treatment is: Non- toxic, Diagnosis and treatment can be done without affecting the healthy tissues and Surface plasmon resonance

2. THERAPY

In radiation therapy, energy is deposited in the target area, damaging the cancer cells or their vasculature inducing tumor death or blockage of nutrients. In chemotherapy, cytotoxic chemotherapeutic drugs are administered to cause cancer cell death through various mechanisms depending on the particular drug used. The combined use of radiation therapy and chemotherapy is being used in cancer treatment. Regardless of the fruitful clinical utilization of consolidated radiation therapy and chemotherapy, the significant limitation of joining chemotherapy and radiation therapy is ordinary tissue toxicity, since either modality can cause significant typical tissue toxicity. Side effects of the treatment can be further minimized through targeted delivery of anticancer drugs and local enhancement of the radiation dose. Gold nanoparticles (GNPs) can assume a critical part in such manner since GNPs can be utilized as radiation portion enhancers and anticancer medication transporters. The high Z-components are utilized to further develop radiation therapy results. Past analyses showed that GNPs upgrade radiation dosages in both the kV and MV range in vitro and in vivo. Notwithstanding, more noteworthy radiation sensitization was seen for cells illuminated with lower energy radiates (kV) than with higher energy radiates (MV). Notwithstanding, megavoltage energy photons are for the most part utilized in radiation therapy, since they can arrive at tumors found profound inside the patient.

3. BLEOMYCIN

GNPs can also be used as an anticancer drug carrier. Here Bleomycin (BLM) has been chosen as the anticancer drug. Bleomycin (BLM) is one of the most potent natural anti-tumor drugs and has been used for chemotherapeutic agents in clinical treatments. The therapeutic effectiveness, however, is limited due to the side effects of the drug, most notably pulmonary toxicity. Bleomycin ties to the DNA and causes the loosening up of the twofold helix and produces reactive oxygen revolutionary species that cause DNA strand breaks. The sulfate finishing of bleomycin joins to the outer layer of GNPs and this straightforward formation makes it an optimal medication to use in a combinational report experiment.

In this paper, GNP - interceded chemo-radiation is tried for a radiation wellspring of 6 MV utilizing an in vitro bosom disease cell model. MDA – MB – 231 were used because it is observed that these cells have relatively good GNP uptake and significant radio- sensitization. MDA-MB-231 cells are also a triple negative cell line that is known to be more aggressive, highly invasive with worse prognosis. In addition, MDA-MB-231 cells express high levels of integrins, including αvβ3 receptors and are targeted by integrin-binding proteins that will be used to modify the surface of GNPs in this study. It is likewise vital to consider the size of the GNP platform since they range from 1 to 100 nm. More modest GNPs include a superior penetration inside the tumor grid, albeit the highest take-up at the cell

level was viewed as for GNPs of width 50 nm. One of the approaches to uptake smaller nano particles is by conjugating the particle with a peptide sequence containing integrin-binding domain, RGD.

4. METHODS

Synthesis and surface modification of gold nanoparticles:

Gold NPs of size 10 nm were synthesized using the citrate reduction method. GNPs were first balanced out with pentapeptide (300 peptides/GNP). The grouping of the pentapeptide is Cys-Ala-Leu Asn-Gracious (CALNN). The peptide with RGD space was added to the CALNN settled GNPs with a proportion of 16-20 peptide/GNP. The sequence of the peptide containing integrin-binding domain, RGD, is H–Cys–Lys–Lys–Lys–Lys–Lys–Lys–Gly– Gly–Arg–Gly–Asp–Met–Phe–Gly–OH (CKKKKKKGGRGDMFG) sequence. This RGD peptide-altered GNP develop will be marked and alluded to as GNP-RGD. Bleomycin was added onto GNP-RGD with a proportion of roughly 780 bleomycin particles/GNP. Presently it is alluded to as GPD - RGD - BLM.

Quantification of GNP uptake incells

GNP uptake in cells was quantified using inductively coupled plasma atomic emission spectroscopy (ICP- AES). Cells were processed with aqua regia in a silica oil bath for 2 h. Samples were diluted and concentrations of gold (Au) atoms were measured in mg/L.

Clonogenicassay

After treatment, the cells were trypsinized and seeded for a certain number of days for it to form colonies. For MDA – MS – 231 cells were grown in culture for period of 10 to 14 days. After the colonies were formed methylene blue was added to stain them for counting. The survival fractions of treated cells were determined using the ratio of the number of colonies formed/number of cells seeded × plating efficiency.

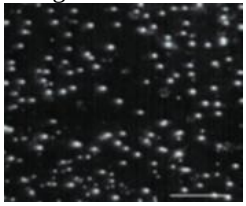
Radiationtreatment

The cells that are grown are incubated with the GNP hours before irradiation with a 6 MV X-rays.

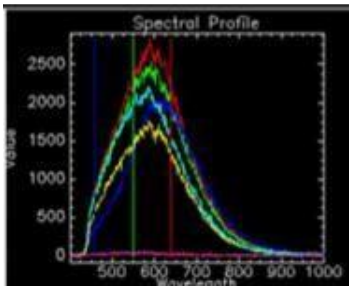
5. OBSERVATION

Cellular accumulation of NPs modifiedwith peptide containingin tegr in binding domain, RGD:

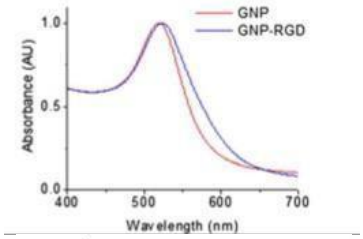
Hyperspectral imaging technique was used to image GNPs and GNPs in cells. Below is a hyperspectral image of 10 nm GNPs where the bright dot-like structures are GNPs

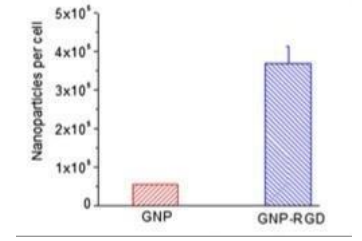


Reflectance spectra collected from the bright pixels were confirmed to be GNPs as shown below



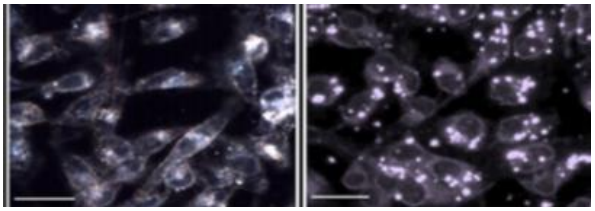
UV visible peak wavelength of unmodified GNPs was 517 nm as shown below and this is consistent with the wavelength corresponding to 10 nm diameter GNPs. UV noticeable spectra of RGD peptide formed GNPs (alluded to as GNP-RGD)had slight red shift from 517 to 519 nm. This shift is anticipated to be because of the RGD peptide.





The cellular accumulation of GNP-RGD was compared with the cellular accumulation of unmodified GNPs. There was a six- to sevenfold increase in cellular accumulation for the GNP-RGDs.

The increase in accumulation was visible in qualitative optical images obtained using hyperspectral imaging. The splendid speck like designs were GNP bunches confined inside cells.



This integrin-binding domain, RGD, is one of the principle adhesive ligand. Hence, the significant increase on six- to sevenfold in accumulation for RGD modified GNPs can be predicted to be due to enhanced coupling of GNP complexes with cell surface receptors. The accumulation of GNP constructs is known to be cell line dependent.

The difference in accumulation between different groups of cell line is because normal cells form tight intra-connected colonies and therefore, NPs can be internalized mostly only at the edge of a growing colony, while in malignant cells, the cell–cell and the cell–matrix connection is disturbed and therefore, NPs can be internalized into anycell.

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Radiation therapy using RGD peptide modifiedGNP:

The cells brooded with GNP-RGDs preceding the radiation had a 19 ± 6% lessening in cell endurance division contrasted with the control cells (without any GNPs). This significant decrease in cell survival fraction could be due to the six- to sevenfold increase in GNP accumulation. Enhancement in cell killing in the presence of GNPs during a radiation treatment is due to the production of larger number of free radicals that can damage DNA lowering their survival.

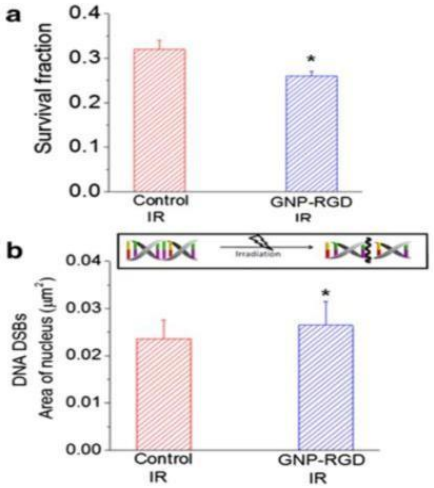
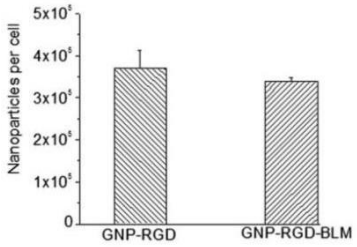


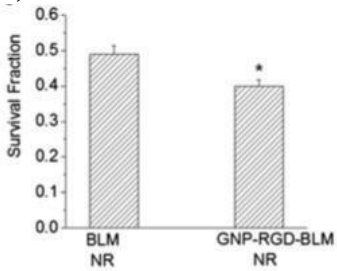
Figure a. shows the survival fraction and figure b shows the double strand breaks(DSB) before and after treating with GNP –RGD.

Drug delivery using goldnanoparticles:

Subsequent to altering the GNP-RGD complex with BLM, the aggregation of GNP-RGDBLM edifices in cells didn't vary from the gathering of GNP-RGD buildings



Cells treated with GNP-RGD-BLM had a 18 ± 4% reduction in tumor cell endurance contrasted with the gathering that were brooded with a similar measure of the free medication, BLM



The essential activity is to create single-and twofold strand breaks in DNA, through a deoxyribose oxidation step that is like the free extreme harm delivered by GNPs within the sight of radiation.

GNP-mediated combinedtherapy:

The next approach is to test the GNP constructs in combined use of radiation therapy and chemotherapy. The standard treatment protocol is to inject chemotherapeutic drugs to the patients prior to the radiation treatment. Here, the cells were first treated with drug-conjugated GNPs (GNP-RGD-BLMs) preceding the radiation therapy. The cells treated with GNP-RGD-BLM and radiation (alluded to as IR GNP-RGD-BLM) had a 32 ± 9% reduction in cell endurance contrasted with the cells treated with free bleomycin and radiation (alluded to as IRBLM)

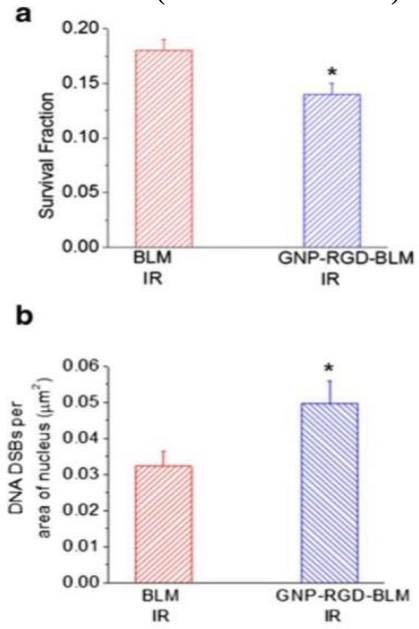


Figure a shows the survival fraction and figure b shown theDNA – DSB after passingradiations.

The summarized results of radiation therapy, chemotherapy, and combined therapy are shown below

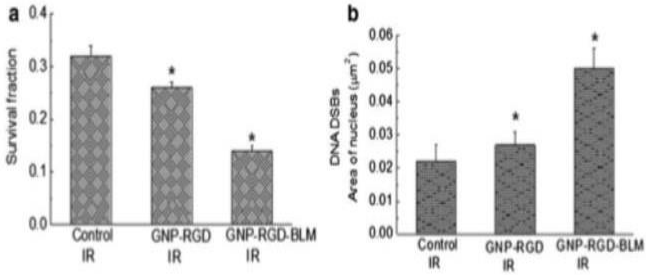


Figure a shows the survival fraction and figure b shows the DNA – DSB after passing radiations.

APPLICATIONS

GNPs are also being used in photo-thermal therapy and photodynamic therapy. Consequently, GNP-based multifunctional GNP platform could work with the mix of a large number of remedial modalities for conveying a higher restorative burden to destroy therapeutic resistant tumor cells. With appropriate engineering, these GNP-based platforms have the capacity for controlled delivery of therapeutic doses, while minimizing toxicity to the healthy organs andtissues.

CONCLUSION

The GNP-based platform proposed in this paper has the potential for delivering chemotherapeutics more efficiently than free drugs, while at the same time acting as a radiosensitizer. Introduction of anticancer drug carrying GNPs into the radiation treatment protocol would give rise to 32 ± 9% decrease in tumor cell survival fraction and statistically significant increase in DNADSBs.

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