RADIOSENSITIZATION BY NANOPARTICLES

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1. Introduction:

After cardiovascular diseases, cancer is the second leading reason of death all over the world[1]. More than the physiological burden which leads to mortality, the emotional toll imposed to the patient and on their well-wishers is even more distressing. Cancer is basically a cluster of diseases which cause an unbalanced and uncontrolled cell division without responding suitably to the signals that regulate the cell behavior, ultimately scattering to other regions of the body. Blooming of a multi-cellular organism in any environment rely on the harmonized occurrence of all the cellular tasks in congruity of the rules that standardize every essential biological process for the cell growth and reproduction. In spite of the significant advancement in the therapeutic industry, cancer is still an alarming disease throughout the world. As per the International Agency for Research on Cancer (IARC) and World Health Organization (WHO) the total number of new cancer case is estimated to have amplified to 19.2 million and 9.9 million demises in 2020, globally[2]. Out of which, 5.8 million (58.3%) deaths occurred in Asia itself. With this rate the estimated new cases from 2020 to 2040 of both the sex will be around 30.2 million[3]. The mortality rate due to cancer in India has doubled from 1990 to 2016 and is further expected to be doubled by 2040[4]. Thus novel stratgies are required for the early diagnosis and effective treatment of cancer.

There are quite a few treatment modalities practiced for cancer therapy depending upon the site of disease, its grade (highly proliferative or slowly progressing) and stage. The final aim is to make the most of the cancer cell killing efficacy with least amount of side effects to the nearby normal tissues[5]. Among all, surgery, chemotherapy, and radiation therapy (RT) are the most prevalent modalities for cancer treatment[6]. Radiotherapy (RT) alone or given in association with surgery and chemotherapy has been used as a major path of treating cancer since the discovery of X-rays by Röntgen in 1895 and used for more than 60% of all cancer patients which kills the cancer cells[7].The three fundamental discoveries, first X-rays in 1895 by Röntgen, natural radioactivity by Becquerel in 1896 and isolation of radium by M. Curie in 1898, paved the ways for two major techniques for radiotherapy namely,teleradiotherapyandbrachytherapy.. In general, the radiotherapy is nothing but delivery of highly energized photons to the tumor site with high accuracy which results in cell

death[8].This high energy radiations(alpha, beta, proton, neutron and electrons) cause ionization in the cellular components or waterpresent in it[9,10].The cellular damage is done by both direct as well as indirect mechanism in radiotherapy. In direct way, the incident beam directly breaks the double helix of DNA and causes the cell death by apoptosis or necrosis whereas in indirect mechanism the high energy radiation interacts mainly with oxygen containing molecules to generate numerous reactive oxygen species (ROS)[11]. Water being the most important part of cellular component, it gets radiolysed by the ionizing radiation to produce various free radicals (hydrogen, hydroxyl radical, superoxidesetc) along with charged species like H_2O^+. These reactive oxygen species interact with DNA to damage them. These free radicals also cause destruction to the structure of cellular membranes which leads to the induction of apoptosis which is known as lipid peroxidation[12]. In spite of great advancement in radiation oncology for focused ionizing radiation and their subsequent dosing for enhanced therapeutic outcome, still some challenges remain. Sometimes it is found that the cancer site is far away from the source of radiation and hence receiving very low intensity of dose than required. This makes the radiation therapy utterly ineffective which in tackling the tumor regression. Some tissues are also observed to develop resistance to radiation and becoming non-responsive towards the radiation dose given to it. Now there are three major pathways to augment the effectiveness of radiotherapy which are summarized in figure 1 below namely a) increasing the radiosensitization of the tumor tissue, b) enhancing the radioresistance of the healthy tissue and c) reversing the radiation resistance of of tumor tissue.

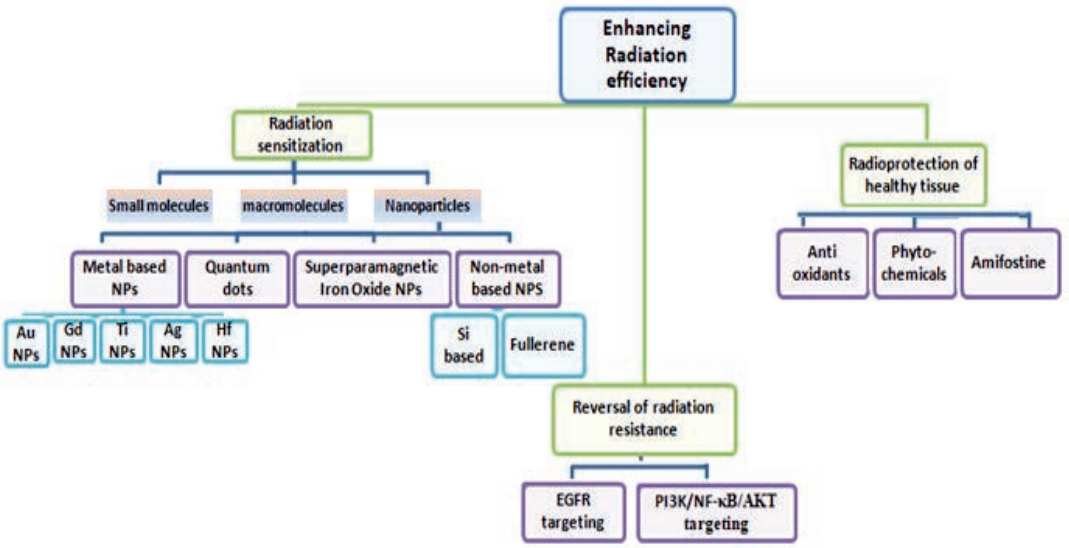

Fig. 1 Different approaches for increasing effectivity in radiation therapy

2. Radiosensitization:

Radiation sensitization involves improving the sensitivity of tumor tissues to radiation exposure in order to increase its effectiveness as a treatment. Consequently, radio sensitizers are substances that either have therapeutic properties or are inert but can amplify the impact

of radiation therapy. Radio sensitizers are exogenous substances that enhance the benefits of radiation treatment while simultaneously minimizing the adverse effects on surrounding healthy tissues[13]. Selective sensitization, chemical stability and slow metabolism, effectiveness throughout the cell cycle, and efficacy at modest daily doses of radiation are all qualities that ideal sensitizers ought to possess. The dose enhancement factor (DEF) or the sensitizer enhancement ratio (SER) is most frequently used to characterize the comparative effectiveness of a specific cell radio-sensitizer. The ratio of radiation dose when used alone vs in the presence of the cell sensitizer to achieve the same physiological impact is represented by the SER and DEF. If the number was greater, the accumulation of the agents would act as a radio-sensitizer and if its zero or less, the medication functions as a radioprotector. In recent years, a substantial rise in curiosity regarding the utilization of formulations to enhance the therapeutic effects of radiation by employing different sensitizer moieties has been observed which in particular have the ability to absorb or scatter high-energy gamma/X-ray radiation in selective manner. There has been a lot of interest lately in adopting cutting-edge formulations to improve the outcomes of radiation, particularly the use of metal-based nanoparticles[14-16]. According to their structural characteristics, radiosensitizer agents can be categorized into three groups: small molecules, macromolecules, and nanomaterials. Macromolecules including miRNAs, proteins, peptides, and oligonucleotides can increase radiation sensitivity in addition to tiny molecules and nano-radiosensitizers. Several strategies, including the use of super paramagnetic iron oxides, metal-based nanoparticles (NPs), quantum dots and non-metal-based NPs, have been suggested to increase the radiation dose to the tumor[17-21]. Due to their distinct physical and chemical properties, NPs, particularly those made of noble metals, have been proposed as a potential means of enhancing the effectiveness of RT techniques. New and excellent tools for cancer imaging, diagnosis, and treatment have been made possible by radio-sensitizers. Numerous NPs, including gold, bismuth, iron, titanium, and carbon, have been proposed as probable thus far. In the current survey, we thoroughly analyzed these tactics.

3. Historical perspective of nanoparticles based Radiosensitization:

Herold, Das, Stobbe, Iyer, and Chapman (2000) reported the first instance of radiosensitization to gold particles that occurred both in vitro and in vivo[22]. They used 1.5–3.0 micron diameter gold particles in their groundbreaking investigation. The potential for the colloidal gold solution to sensitize various cancer cells such as human prostate cancer cells, mouse tumor (EMT-6) and Chinese hamster ovary cells was investigated.When exposed to a kV X-ray source in vitro, all cell lines displayed considerable sensitization with an average increase in cell death of 1.43. The in vivo investigation involved inoculating mice with EMT-6 cells, giving them three intratumoral injections of gold microparticles, and then giving them 8.0 Gy from a 200 kV X-ray source. Microscopical analysis and clonogenic experiments were performed on ex vivo tumor tissue. Only in interstitial fluid was a highly heterogeneous distribution of gold particles seen. Despite this, a noticeable effect on tumor cell viability was obtained. Homogeneous administration to solid tumors would still be difficult and that colloidal high-Z materials were necessary for the practical translation of such radiosensitizers in order for them to be effective. That is why it is important to look into gold particles that are

considerably smaller (less than 2 nm) and other particles that have been linked to tumor antibodies and other substances. The conclusions have turned out to be extremely opportune for being the first publication in this sector. In a paper published in 2004, Hainfeld, Slatkin, and Smilowitz described the intravenous delivery of 1.9 nm gold nanoparticles (GNPs) to a subcutaneous EMT-6 tumor in mice[23]. Significant tumor growth inhibition was observed when the NPs were administered along with 26 Gy of radiation from a 250 kVp source (Figure 1). The area of study subsequently attracted a lot of interest, which resulted in a variety of papers on various mechanisms, nanoparticles, and medicinal sources.

4. Radiosensitization by nanoparticles:

Owing to the calculations showing that high-atomic-number (Z) nanoparticles exhibit improved properties by the incoming enhanced radiation dose deposit, their usage in radiotherapy has gained increasing attention. Due to their special characteristics of a high photoelectric cross-section (Z^3/E^3, Z atomic number, E incident energy), nanoparticles with high-Z enhance the radiation dose deposit into malignant tissues[24]. There have been an increasing number of studies employing high-Z NPs applied as radiosensitizers, such as gold (Au), hafnium (Hf), bismuth (Bi), gadolinium (Gd), and silver (Ag) NPs.

4.1. Physical effects:

The fundamental justification for increase of biological responses is that high atomic number metal has a greater radiation stopping ability compared to soft tissue. When radiation is interacting with matter three major incident happens namely, Compton effect, photoelectric effect and pair production (Fig 2).High-Z metal nanoparticles have the ability to cause more energy deposition to the cancer tissue[25,26]. After the collision of photon with weakly bound electron through Compton scattering, the electrons lose some of their energy and are propelled out of their orbit. After losing some of its energy, the incident photon scatters simultaneously. More interactions between the photon and the electron cause the surrounding tissue to become ionized.In pair production, there occurs an interaction between photons and atoms's nucleus.The likelihood of pair creation rises according to Z^2 and photon energy. This interaction seldom ever happens in standard radiation therapy pair formation predominates usually at higher than 25 MeV.The material mostly experiences the photoelectric effect when it interacts with ionizing radiation of relatively low energy (60 keV). After receiving all of the photon energy, an electron in a tightly bound innner orbit quickly departs from it. The electrons that are rejected are referred to as photoelectrons, and the incident photons disappear. This occurrence causes the outer shell electron to be transferred to open space and releases secondary radiation, sometimes referred to as fluorescence photons, with a wavelength determined by the difference of energy of two orbits involved. An Auger electron can be released when an outer shell electron fills an inner shell vacancy produced by the photoelectric effect[27]. The Auger electron can be extremely hazardous to cells due to its extremely high linear energy transfer (LET)[28]. The likelihood that the photoelectric effect will occur rises noticeably as atomic number of absorber (Z^3) grows, and falls noticeably as input photon energy (E^3) rises. In other words, Z^3/E^3 is proportional to the photon mass attenuation coefficient. Therefore, through photoelectric processes, photoelectrons, secondary photons,

and Auger electrons released by metal nanoparticles with high atomic number will lead to highly localized dose increase and focal ionization of neighboring cells (Fig. 2) [29,30].

Accurate prediction of the optimal dose can be achieved by simulating all the interactions involved. The prediction takes into consideration a number of factors, including as element variation in the irradiation field, beam attenuation, and secondary particle distributions caused by interactions with soft tissue. Many specialized tools have been developed to facilitate radiation interactions with matter in Monte Carlo simulations[31-33].

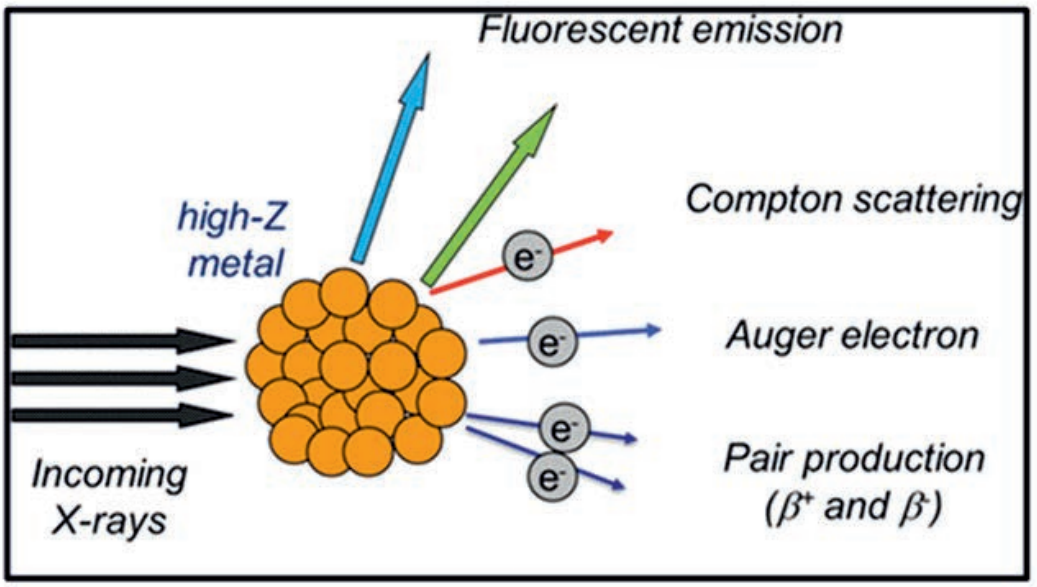

Fig. 2 Diagram showing the interaction of X-rays with High Z substances "Reprinted with permission from {Kamkaew, A., Chen, F., Zhan, Y., Majewski, R.L. and Cai, W., 2016. Scintillating nanoparticles as energy mediators for enhanced photodynamic therapy. ACSnano, 10(4), pp.3918-3935} Copyright (2016) American Chemical Society" Ref 24.

4.2. Biological effects:

Oxidative stress, cell cycle effect followed by DNA damage and bystander effect are majorly observed biological processes due to the incoming radiation in presence of high Z NPs during radiotherapy (Fig. 3).

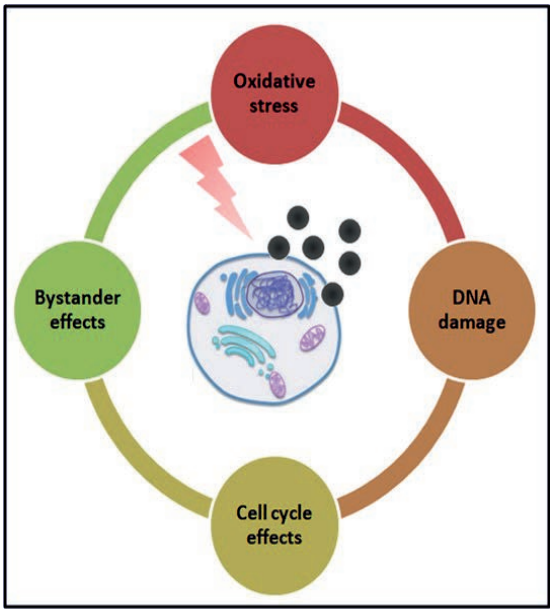

Fig. 3 The biological effects after radiosensitization

4.2.1. Production of reactive oxygen species (ROS):

The main cause of radiation-induced cell death is DNA damage caused by reactive oxygen species (ROS). The oxidative species hydroxyl radical ($OH^{\cdot}$), hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), singlet oxygen ($^1O_2$), and hypochlorous acid (HOCl) are among those that fall within this category. Apoptosis, DNA damage, and oxidative stress are all brought on by ROS, which is formed when radiation interacts with a substance and generates electrons (Fig. 4)[34,35]. According to reports, high-Z metal NPs produce high levels of ROS and damage DNA by oxidation[36-38]. Choi et al. have created a ROS sensor (dihydrorhodamine 123) connected to gold nanoparticles, allowing for assessment of ROS production by gold nanoparticles. It was discovered that 6 Gyradiation increased the production of ROS by gold nanoparticles by a factor of seven[39].

4.2.2. Effect on cell cycle:

Depending on the various cell cycle phases, radiation exerts varied biological effects. The least radiosensitive cells are those in the S phase, whereas the most radiosensitive cells are those in the G2-M phase[40]. The p53 is activated and gets phosphorylated by the activation of ataxia-telangiectasia mutated (ATM) kinase after the successful splitting of DNA double helix by the hydroxyl radical.At subsequent step the p21 gets activated by the P53 protein. Cell cycle gets arrested in G1 and G2 phase after the over expression of cyclin-dependent kinase (CDK) inhibitor[41-43]. It has been claimed that radiosensitization is obtained by inducing cell cycle arrest using metal nano particles with high atomic numbers.

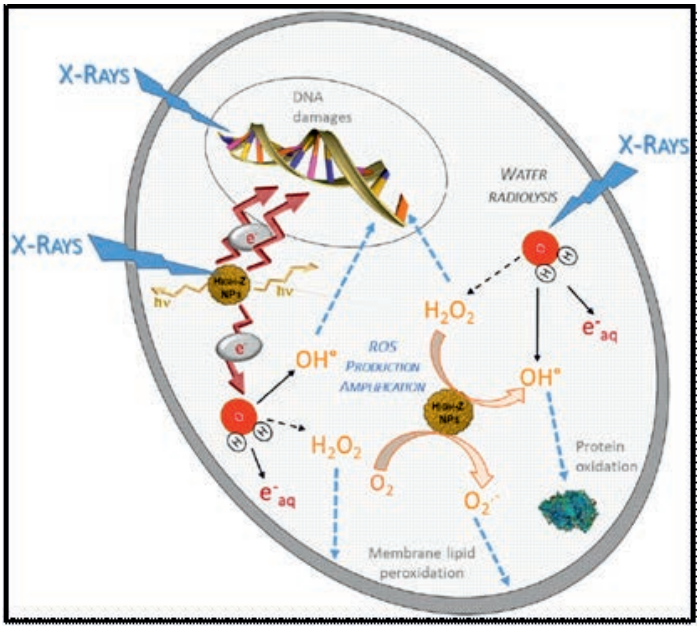

Fig. 4Schematic illustration of the mechanism ofinteraction between incident photons and high-Z NPsin a biological system (Adapted from Ref. 38Creative Commons CC-BY license, © 2018 by authors, Published by Elsevier B.V.)

4.2.3. DNA damage and bystander effect:

The key machinery of radiotherapy-mediated cell death is breaking of DNA double strand by induction of radiation. According to a number of studies, metal nano particles with high atomic numbers can cause harm to DNA and limit refurbish during radiation. By γ-H2AX measurement during irradiation, Chithrani et al. found that gold nanoparticles (50 nm)caused a larger number of DSB[44]. In the human colorectal cancer model, Marill et al. found that radiotherapy-activated hafnium oxide NPs increased DNA damage compared to radiotherapy alone[45]. Intercellular communication can also help radiotherapy work well[46,47]. According to Fujiwara et al., titanium dioxide NPs may increase the production of inflammatory cytokines[48].

4.3. Different types of nanoparticles for radiosensitization:

In this section diverse types of nanoparticles based radio sensitizers are discussed in brief.

4.3.1. Metal based nanoparticles (Hf, Gd, Au, Bi, Ag):

The element hafnium (Hf), which has a high Z value of 72 and the ability to emit electrons, is used to create X-rays. This element has exceptional processability, corrosion resistance, high-temperature resistance, and plasticity (stretchability). Hafnium oxide NPs' capacity for radiosensitization has been documented in a number of in-vivo and in vitro experiments[49-50]. Because of their high electron density, functionalized hafnium oxide nanoparticles can better absorb ionizing radiation and deposit more energy inside tumor cells. When Hf-doped hydroxyapatite nanoparticles were exposed to gamma rays, more ROS were produced in the tissue, which ultimately led to the demise of cancer cells[51].

Another element with a high atomic number z is gadolinium (z = 64), which has a high coordination number of eight to ten. The advantages of gadolinium-based NPs are their high permeability, high biodistribution, high relativity, and passive uptake in tumors. Gadolinium oxide nanoparticles with hyaluronic acid functionalization were employed by Wu et al. for MRI and radiosensitization of malignancies. The endocytosed nanoparticles (NPs) through hyaluronic acid receptors exhibited favorable biocompatibility, low cytotoxicity, and good dispersion in aqueous solutions. The gadolinium oxide NPs increased apoptosis and stopped the cell cycle, which permitted the radiosensitization of tumor cells[52].

A new variety of gadolinium-based nanoparticles with diameter around 5 nm, known as AGuIX (NH TherAguix, France) were created by Mignot et al. for radiosensitization[53]. Hu et al. employed radiation sensitivities from AGuIX to assess tumors and carry out radiation therapy for hepatocellular carcinoma (HCC).In this formulation, the Gd effectively has enhanced the ratio of dose deposition and radiation sensitivity[54].

Gold nanoparticles have been broadly researched as tumor radiosensitizers for having several advantages. It is highly biocompatible because of its high inertness. It is no longer necessary to administer the nanoparticles to each and every cell in the tumor tissue because the gold nanoparticles disperse the radiation's effect over a greater portion of the tumor. As compared to utilizing iodine solutions, a lot more gold atoms may be supplied selectively to the tumor tissue by attaching targeting moieties like antibodies. To achieve the best possible delivery and effect, gold nanoparticles can be fabricated into a broad variety of shapes and sizes, including spheres, cubes, rods, cones, and other three-dimensional structures. This can be done by taking into account the size and location of the tumor tissue. To investigate the impact of radiation and gold nanoparticles in certain malignancies Joh et al. investigated how gold nanoparticles affected the sensitivity of glioblastoma tumors[55]. They discovered that the gold nanoparticles greatly increased brain endothelial cell mortality in addition to amplifying the radiation effects in vitro. When given the medication, mice with orthotopic glioblastoma multiforme tumors had a higher survival rate. Recently our group has shown the efficacy of lanreotide peptide (LP) conjugated gold nanoparticles for the selective delivery towards somatostatin receptor 2 (SSTR2) expressing tumor tissues[56]. The size of NPs determines how lethal they are as radiosensitizers.[57-59]. The effect of gold NPs larger than 30 nm was same to that of 13 nm, although their toxicity was increased[60]. Polyethylene glycol (PEG)-coated nanoparticles (13 nm) have been used to improve the quality of CT scan imaging and radiosensitization[60]. Among other high Z-NPs , Bismuth (Bi, 83) and Silver (Ag,47) based are prime due to their low toxicity and biocompatibility[61]. Additionally, bismuth nanoparticles made from cellulose nanofibers were effective at destroying tumors because they boosted the synthesis and secretion of free radicals when exposed to X-rays. The bismuth nanofibers' carbonyl groups allowed them to be efficiently absorbed and prevented local oxidation, which made them biocompatible. Similar to gold nanoparticles, silver nanoparticles also exhibit radiosensitizing characteristics and work through comparable mechanisms. Chitosan-coated triangular silver nanoparticles were shown to have a higher radiosensitizing effect on human non-small lung cancer cells than conventional PEG-coated gold nanoparticles[62].

4.3.2. Quantum dotnanoparticles:

Due to their small size, quantum dots derived from semiconductor materials that exhibit quantum mechanical features which were first identified in the early 1980s were explored for biological applications. Radiosensitizer applications for quantum dots consisting of ZnS, CaF, LaF, or ZnO have been proposed[63]. The creation of photosensitizing quantum dots has attracted a lot of attention[64]. These quantum dots could produce free radicals in the presence of visible light which is less hazardous as compared to high energy ionizing radiations.

4.3.3. Superparamagnetic iron oxide nanoparticles:

Magnetite (Fe_3O_4) or maghemite (Fe_2O_3) make up the majority of superparamagnetic iron oxide nanoparticles. These are also well known for being highly biocompatible and for not harming healthy tissues in any way, which makes them appropriate for use in therapy[60]. They spoil the DNA by the formation of ROS (oxidative stress)[65]. Fe_3O_4/Ag was combined with an antibody (C225) that is specific for the epidermal growth factor receptor to create a multifunctional nanocomposite. This composite can function as both radiation sensitizer and a diagnostic tool for MRI[66].

4.3.4. Non-metallic nanoparticles:

The potential role of silica nanoparticles in radiosensitization has been investigated. Klein and associates investigated radiosensitization effects of functionalized silica nanoparticlesin murine fibroblast cells (3T3) and breast cancer (MCF-7) exposed to 3 Gy X-rays[67]. Early in the 1990s, scientists discovered the fullerene C60, which has a singular globular structure. Strong anti-cancer properties of fullerene C60 are associated with the induction of certain autophagy-related markers in cancer cells[68-70].

5. Summary and perspective:

Conventional radiation therapy is anticipated to be transformed by the development of nanoparticles having high atomic numbers (Z) as radiosensitizers with salient features.The complexity of the various factors involved makes it difficult to identify and compare similar mechanisms that support the generation of ROS. There are still significant obstacles because cellular internalization and destiny vary greatly among different kinds of cell population. Understanding the precise mechanisms underlying each therapy approach is essential for their clinical use, as understands how they work in concert. Our ability to get a deeper understanding of the mechanisms behind radiation therapy has been constrained by our lack of understanding of thorough intracellular processesafter radiation interaction.Even with significant advancements, not much research has been done on how radiosensitizers interact with newly created therapeutic approaches like gene delivery and sonodynamic therapy. It is therefore strongly advised to conduct basic research in order to optimize the therapeutic potential of metal nanoparticle radiosensitizers.

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