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Original Article

Selective Radioprotection of Normal Tissues by Nanoparticles: Antioxidants as Radioprotectors, Radiation's Negative Effects, and New Approaches to Radioprotection

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Abstracts: Ionising radiation is used in radiation therapy to destroy cancer cells; nevertheless, there are negative side effects to this treatment. The harmful effects of radiation on healthy tissue can be mitigated with the use of some radioprotective medications. Multifunctional nanoparticles have recently gained a lot of attention due to the growing interest in nanotechnology in the biological sciences. These particles serve multiple purposes, including improving molecular radioprotective drugs through improved drug delivery systems and opening up new avenues for the development of radioprotective agents, as some nanoparticles already have these properties. When used to the medical field, nanotechnology is known as nanomedicine. In its most fundamental form, nanomedicine refers to two ideas. On the one hand, it's described as a field that applies molecular tools and human body knowledge to medical diagnosis and treatment. On the other hand, it's described as the application of physical effects on nanoscale objects at the interface of the molecular and macroscopic worlds, where quantum mechanics is taken for granted. The late Nobel laureate physicist Richard P. Feynman was the first to express his vision for the numerous medical uses of nanotechnology; he foresaw the implantation of microscopic surgical robots. By bringing together nanotechnology and biology, we can solve many biomedical problems and transform healthcare, as the vast majority of natural processes occur at the nanoscale. Nanoscale inorganic and organic particles can be biologically modified to serve as a sensor, imaging tool, gene delivery system, artificial implant, targeted drug delivery, and other medical applications.

Keywords: Nanoparticles, Selective Radioprotection, Normal Tissues.

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Introduction:

Radiation experts have known since the beginning of the nuclear age that astronauts' space travel, nuclear accident radiation exposure, and countermeasures for radiation terrorism all necessitate the use of technology that protects normal tissues during radiotherapy while exposing tumours to radiation. Radiation therapy is an integral part of the multidisciplinary approach to cancer treatment, with over 50% of patients undergoing some sort of radiation treatment [1-3]. The hunt for such agents has continued for over 60 years, but so far only one molecule, amifostine, has found limited usage in therapeutic settings.

To be an effective radiation protector or mitigator when used in conjunction with cancer radiotherapy, a radiation shield should meet the following criteria: (1) reduce radiation's toxic effects to a clinically meaningful level; (2) maintain radiation's antitumor efficacy; (3) have an acceptable toxicity profile; and (4) show a favourable cost/benefit ratio. Antibiotics, cytokines, nanoparticles, calcium antagonists, adenosine analogues, methylxanthines, superoxide dismutase, Chinese herbal medicines, thiols, nitroxides, inhibitors of angiotensin-converting enzyme, protease inhibitors, antioxidant vitamins, metalloelements, and the current pipeline of potentially useful agents or combinations of agents is growing. Radiation causes cells to produce reactive oxygen species (ROS), which cause irreversible damage to DNA and RNA and ultimately cell death. There have been significant advancements in targeting the tumour with radiation using techniques like proton therapy or intensity modulated radiotherapy. However, this method still has the drawback of damaging healthy tissue around the tumour. As a result, patients may experience many of the side effects commonly linked to radiation, including gastrointestinal issues like nausea, vomiting, diarrhoea, and dry mouth, as well as inflammatory effects like mucositis and pneumonitis, kidney failure, demyelination of the central nervous system, dermal fibrosis, and telangectasia, as well as behavioural disturbances like excessive tiredness, changes in appetite, and changes in taste. Also, certain side effects may be dose-limiting, meaning they won't go away even if you take the maximum recommended dosage. Radiotherapy for cancer has come a long way in the past sixty years, but there is still no way to selectively shield healthy tissues from radiation. Newly published, high-quality histories (Weiss and Landauer, 2009) and reports on the evolution of radiation-protective chemicals attest to the snail's pace of advancement. Drug Administration (FDA)–approved for therapeutic use to prevent radiation-induced normal tissue harm (xerostomia). The selectivity displayed by amifostine was not intentionally achieved; rather, it was one of thousands of compounds tested by the United States military in an effort to safeguard citizens and soldiers from nuclear attacks. Without considering how to prevent protecting malignant tissue, the goal of the research was to develop a chemical that would protect normal tissue. Dephosphorylation is necessary for the conversion of amifostine, a small molecule phosphoro-thioate prodrug, into its active thiol form; this form functions as an antioxidant, reducing cell damage caused by reactive oxygen species (ROS). Because the active thiol form accumulates preferentially in normal cells compared to malignant cells, amifostine selectively protects normal tissue. Two things are thought to be responsible for this: first, the lower pH in the tumour microenvironment, which causes alkaline phosphatase to be less active, and second, the reduced cellular uptake of the active thiol. The clinical usage of amifostine is severely restricted by a number of factors. Above all else, it comes with a hefty dose of negative consequences. Some of the most common amifostine side effects include low calcium levels, nausea, vomiting, sneezing, hiccups, somnolence, and diarrhoea. Furthermore, while it works well when given orally to mice and other small animals, it has the greatest clinical impact when given intravenously to dogs and people. There has been extensive research into small molecule antioxidants since amifostine's development [5–9], but none of them have achieved clinical success due to their effectiveness and selectivity. Consequently, the search for and assessment of novel classes of antioxidants that are compatible with living organisms is an urgent matter.

When it comes to medical material development, the most prominent view on the definition of nanotechnology is probably the most recent guidance from the U.S. Food and Drug Administration (FDA).

This guidance states that the following questions will be asked by the FDA when determining if a product regulated by the FDA contains nanomaterials or otherwise involves the application of nanotechnology: 1. If the final product or manufactured material contains at least one dimension that falls inside the nanoscale range (around 1 to 100 nm). 2. Whether the dimensions of a designed material or finished product cause it to display physical, chemical, or biological consequences, regardless of whether these dimensions are outside the nanoscale range (up to 1 μm). Due to their potentially enhanced in vivo efficacy and drastically different biodistribution and metabolic profiles compared to small molecules or enzymes, nanomaterials like these are of special interest for the assessment of biologically

acceptable antioxidants. As a result, they may be able to be targeted to specific areas for antioxidant treatment and remain there for substantially longer periods of time compared to tiny molecules or enzymes. Curiously, anti-oxidants that are compatible with biological systems have been found in a number of nanoparticles. Numerous metal nanoparticles, including hydrophilic carbon clusters, fullerene derivatives, and nanoceria, have demonstrated antioxidant and neuroprotective properties. Nanoparticles [10–12] have showed antioxidant strength, but they haven't shown much selectivity for protecting cancer cells over normal cells or tissues.

Radioprotectors and Radiation

Depending on the exposed and absorbed dose, period of exposure and the time after exposure, and the vulnerability of 10 tissues, ionising radiation (also known as particle radiation) produces ions as it passes through matter and interacts with living cells, causing a range of alterations. Damage to DNA and cell membranes is one of the primary chemical effects of ionising radiation on living tissues. There are several areas of human life where ionising radiations are encountered. Around 80% of human exposure to radiation comes from naturally occurring background radiation, which is present all the time. The medical field makes extensive use of radiation for a variety of objectives, including the employment of radiopharmaceuticals in diagnosis and treatment, radiation therapy for cancer, sterilisation of medical equipment and food products, and many more [13, 14]. radioactive elements have many practical applications in industry, including the discovery of oil and minerals, the fabrication of semiconductor chips for computers, the generation of electricity in nuclear power reactors, and the use of radiocarbon dating to determine the age of objects. The exposure of living beings to radiation and radiation-induced damages has been enhanced due to the extensive use of radiation in diagnosis, therapy, industry, and the energy sector, as well as accidental exposure during air and space travel, nuclear accidents, and nuclear terror strikes, among other causes. Radon exposure to people during diagnostic and therapeutic CT scans and X-rays has the potential to induce cancer, according to recent studies. Careful limitation of radiation exposure dangers is necessary for radiation's useful application. Therefore, in any radiation-related clinical setting, radioprotection plays a crucial role. Useful in clinical oncology [15, 16], space flight, radiation site clean-up, 18 radiological terrorism, and military scenarios, 12 exposure lessens the biological consequences of ionising radiation on normal tissues, including lethality, mutagenicity, and carcinogenicity. Reducing levels of radiation-induced free radicals within the cell has been the primary goal of most of the radioprotective chemicals that have been created over the years. Much research has focused on thiol compounds like Amifostine because of their effectiveness in scavenging free radicals. Clinicians presently utilise amifostine, the only radioprotector approved by the Food and Drug Administration (FDA), to lessen the occurrence and severity of xerostomia in patients undergoing radiation therapy for head and neck cancer. Optimal radioprotective doses are frequently associated with toxicity, which is why this drug's application has been less than desired thus far. In light of these possibilities, it is necessary to create a radioprotector that can be used in either a therapeutic or preventive manner, to lessen the harmful effects of radiation on human normal tissue. This would be useful in a variety of planned or unplanned situations involving radiation exposure, such as when cancer patients are undergoing radiotherapy. Ionising radiation can have devastating effects, thus researchers are still focusing heavily on finding and developing safer alternatives. A number of studies have demonstrated that nanoparticles like cerium oxide, yttrium oxide, carbon, etc., can provide protection against radiation damages, and their antioxidant properties have recently piqued the interest of researchers in the area of radioprotection [17–20].

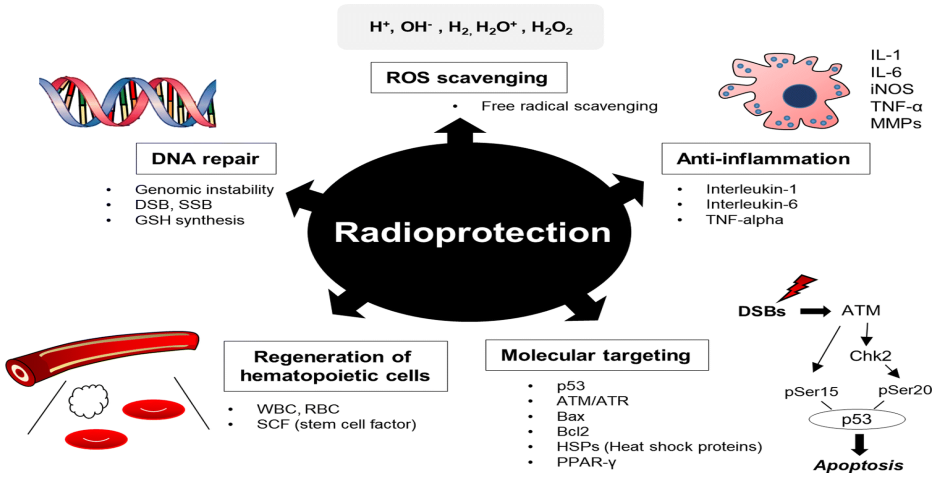

Figure 1. The metabolic pathways of naturally occurring compounds have radioprotective effects. By scavenging free radicals, decreasing inflammation, increasing repair activity, renewing hematopoietic cells, and changing molecular levels, these naturally occurring radioprotective compounds accomplish their several goals.

Use of nanoparticles for radiation shielding:

Nanoparticles are the next big thing in free radical scavenger technology. Nanoparticles made of carbon, ceO2, yttrium oxide, silver, gold, platinum, poly (lactic-co-glycolic) acid (PLGA), etc., have antioxidant and free radical scavenging properties; they could be employed to remove ROS that cause cell damage caused by radiation. Fullerenes are a type of allotropic carbon that exists in compounds with 60 carbon atoms linked by sp-2,5-bonds. Their ability to react with oxygen free radicals and possess an unusual delocalization of þ-electrons makes them useful for controlling free radical processes and alleviating the harmful effects of oxidative stress in living organisms. There has been a lot of interest in fullerenes and their derivatives for biological applications because of their strong reactivity to radicals, particularly ROS such superoxide, hydroxyl, peroxyl, and nitric oxide. In addition to its cardioprotective, hepatoprotective, nephroprotective, and radioprotective properties, water-soluble fullerenes have demonstrated encouraging results in reducing oxidative stress-related neurodegenerative disorders. Multiple investigations have shown that CeO nanoparticles have potential biological uses as radioprotectors and antioxidants. During radiation treatment, the CeO2 nanoparticles save healthy 41 cells from harm. The cerium oxide nanoparticles' intriguing redox chemistry and their appealing radical scavenging 42 capabilities are both caused by the 4+ oxygen vacancies that result from their dual oxidation state (Ce to 3+ Ce) [21, 22]. Additionally, yttrium oxide nanoparticles can protect cells from cellular death caused by oxidative stress. The finding that particles of cerium oxide and yttrium oxide provide protection against oxidative stress can be explained in three different ways. Depending on their mechanism of action, they can either function as direct antioxidants, prevent cells from producing ROS by blocking a stage in the programmed cell death pathway, or directly produce a low level of ROS generation that quickly triggers a ROS defence system. Another possible role for aluminium oxide (Al O) nanoparticles is as free radical scavengers. Silver nanoparticles are an intriguing alternative that demonstrates radioprotective properties due to its exceptional free radical scavenging, antibacterial, and anti-inflammatory actions. Several studies have found that nanocrystalline silver can help with the initial stages of wound healing by reducing inflammation and other inflammatory processes. Due to its malleability, silver nanoparticles can bind antioxidant molecules to their surfaces, creating a conjugate that is far more radioprotective than either component alone. Effective protection of biological systems has been demonstrated in vitro, ex vivo, and in vivo using silver nanoparticle complexes of PAsAG, Glyceryrrhizic acid, sesamol, and lipoic acid. Researchers have found that gold nanoparticles can boost antioxidant defence enzymes by 51 percent and preventing the production of reactive oxygen species (ROS) through scavenging free radicals. It has also been demonstrated that adding gold nanoparticles to antioxidants derived from vitamin E can significantly boost their antioxidant activity.

Biodistribution: A Complex Issue

One major obstacle is the tendency for nanoparticles to accumulate in healthy tissues. The reticuloendothelial system's (RES) clearance and the drug's natural bias towards accumulating in tumour tissue are two big hurdles that must be crossed before normal tissue may be selectively distributed. The red blood cell (RES) pool includes macrophages and other related circulating cells as well as the liver, spleen, lymph nodes, and bone marrow. Microbes and viruses on the nanoparticle size range are the target of the RES's phagocytosis capabilities. So, it shouldn't come as a surprise that the liver and spleen get the bulk of nanoparticles given intravenously [23-26]. In addition, the lymph nodes and bone marrow often contain a tiny quantity. If there is an exception to every rule, it would be Doxil®. The FDA has authorised the use of Doxil, a liposomal version of doxorubicin, in cancer chemotherapy. Because of its exceptional biodistribution profile, Doxil stands out among nanoparticles; the vast majority of compounds never make it to the clinic. However, studies on animals show that the tumour only receives 5% of the injection dose, whereas the liver and spleen absorb around 37%. The first hurdle in successfully localising nanoparticles in normal tissue surrounding an irradiation tumour is ensuring that a sufficient injection dose reaches the target location. One of the key reasons nanoparticles have garnered so much attention for cancer therapy is that, due to the enhanced permeability and retention (EPR) effect, they preferentially accumulate in the tumour microenvironment relative to adjacent normal tissue. Nevertheless, the challenge becomes even more difficult in the local area of the tumour (Matsumura and Maeda

1986). The vascular wall of malignant tissue often lacks or has aberrant perivascular cells and the basement membrane, therefore the blood vessels in this type of tissue are more disorganised, enlarged, leaky, or flawed than those in normal tissue. Consequently, bigger objects, including nanoparticles, are more likely to extravasate from the tumour site's vascular. Furthermore, the nanoparticles remain retained in the tumour for an extended period due to the poor lymphatic drainage in malignant tissues [27-31]. The EPR effect and RES clearance work together to make it very difficult to target normal tissues with nanoparticles.

Radioactive toxicity in animals can cause a variety of unpleasant side effects, including edoema, discomfort, and moderate neutropenia, among others. Additionally, radiation destroys cancer cells by damaging their DNA, which the body then eliminates. The two main modes of interaction between ionising radiation and cells are direct and indirect. When ionising radiations come into close contact with a cell, they destroy it by damaging its DNA. The DNA and macromolecules of the cell are not harmed by radiation in an indirect interaction. Hydrolysis of water molecules occurs as a result of its interaction with intracellular water. The water molecule is split into two parts: the hydrogen atom and the hydroxyl radical. Damage to cell membranes, molecules, and DNA by free radicals can lead to cellular malfunction and eventual cell death. Some people have harmful side effects, such as Acute Radiation Syndrome (ARS), after being exposed to excessive doses of radiation. Radiation sickness, or ARS, can develop when a large area or part of the body is exposed to a significant dosage of radiation quickly. The detrimental effects of ionising radiation on cells, such as an increase in reactive oxygen species (ROS), are immediate and detectable. Another three ways ionising radiation harms cells are by delaying cell division, preventing reproduction, and killing cells in the interphase [32–35]. Apoptotic cells are also found in some malignant cells. Radiation can cause any of these types of cell damage through direct or indirect interactions with cells.

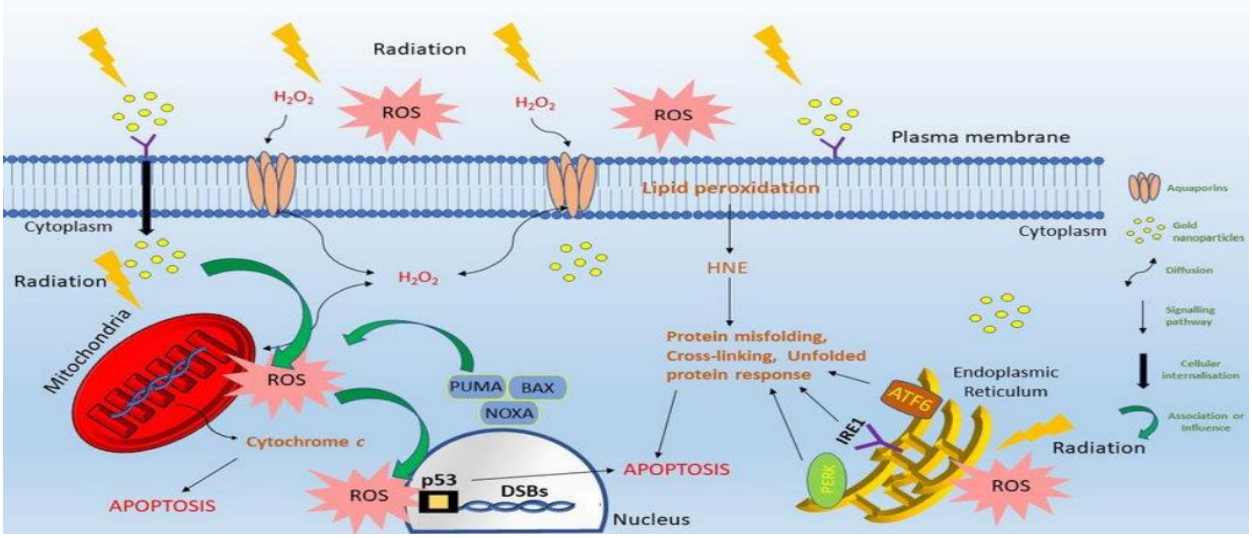

Figure 2. Pathways of reactive oxygen species (ROS), which cause cell death when exposed to ionising radiation.

Radioprotective Antioxidants

In addition to lowering oxidative stress caused by free radicals, antioxidants may improve DNA repair. For instance, phenolic glucoside, a naturally occurring chemical in plants, possesses good anti-radical activity, and antioxidants or compounds that increase glutathione may be able to decrease DNA damage. In vivo, radioprotection is an additional function of many flavanoids, including quercetin, genistein, rutin, and orientin. A few radioprotectors occur naturally in the body; for example, the pineal gland secretes the hormone melatonin. Melatonin mitigates gamma irradiation-induced oxidative damage in the liver. Vitamins A, C, E, and selenium are commonly referred to as antioxidants. By reducing the production of free radicals, they also serve as a radioprotector. Radiation survivorship can be improved by combining vitamin E with WR-3689. Additionally, vitamin E shields cells in the mouth mucosa against radiation treatment for head and neck cancer. Additionally, selenium, when present as selenoprotein, mitigates radiation-induced oxidative stress caused by free radicals. Quercetin, genistein, orientin, and rutin are some of the flavonoids that have radioprotective properties. Radiation of 2 Gy, γ-irradiation can be protected by flavonoids produced at ocimum. All of the body's tissues and medicinal plants contain methylxanthines. Some members of the methylxanthines family include caffeine, theophylline, pentoxifylline, and theobromine. In addition, caffeine shields

mice from 7.5 Gy, γ-irradiation.

The Future of Selective Radioprotection: New Approaches

One way to achieve selective protection of normal tissue is to build nanoparticles so that they aggregate preferentially in normal tissue. Another way is to engineer them such that they are more powerful antioxidants in the normal tissue microenvironment. It is challenging to accomplish selective accumulation in normal tissue, especially outside of the RES system, as mentioned above. it this method has primarily been applied to RES organs in MRI scans so far is indicative of it. An example of a nanoparticle with European clinical approval for liver-specific MRI contrast enhancement is ferucarbotran, also known as Resovist®. It is a superparamagnetic iron oxide (SPIO). Eighty percent of the administered dose of ferucarbotran reaches the liver within minutes of injection, while five to ten percent reaches the spleen. By weakening a certain MRI signal component (T2), SPIO particles serve as contrast agents for magnetic resonance imaging (MRI). When ferucarbotran is accumulated by phagocytic cells, the MRI signal in healthy spleen and liver tissue is reduced [36, 37]. In contrast to the hypointense, black liver, hyper-intense, brilliant lesions characterise malignant tumours, which typically lack substantial numbers of phagocytic cells. Clinical trials have expanded this approach to address lymph-node metastases in prostate cancer. Nanoparticles may be delivered to normal RES cells without causing tumour accumulation, according to the available evidence. No reports of this method combining radiation therapy with radioprotective nanoparticles for the treatment of RES tumours have been found so far. We anticipate the continuation of these kinds of research and hold out hope that they may lead to more effective treatments for various tumour types. We need to change our approach if we want to use a preference accumulation technique outside of the RES system. Nanoparticle surface modification with poly(ethylene glycol) to promote blood circulation and limit RES clearance and antibody conjugation to the particles to attach to the target tissue is the principal technique for modifying nanoparticle biodistribution. So far, most studies have focused on developing antibodies that can attach to cells within the tumour microenvironment. Antibodies that target normal tissue but not malignant tissue are in short supply. Nevertheless, a case of pancreatic cancer imaging utilising this method does exist in the imaging literature. While pancreatic ductal cancer showed reduced levels of bombesin peptide binding receptors, normal pancreatic tissue showed significant levels. Next, MRI contrast agent nanoparticles were functionalized with bombesin to make them more attractive to normal pancreatic tissue for binding. In a mouse model, this led to a significant improvement in the identification of pancreatic cancer. Radiation therapy combined with radioprotective nanoparticles directed at healthy tissue has not been tried for the treatment of pancreatic cancer or any other tumour type as far as we are aware [38–41].

The last tactic for targeted radioprotection is to employ nanoparticles, which are naturally stronger antioxidants in healthy tissues than in malignant ones. If the issue of selective biodistribution cannot be resolved, it will be of little consequence in this way. Selective protection will take place because the nanoparticles in healthy tissue are substantially more active than those in malignant tissue. Although the mechanisms underlying the increased potency are unclear or unknown, there are multiple findings in the literature on this developing technique. To shield bone marrow from radiation treatment in a melanoma mouse model, one study used melanin-coated silica nanoparticles. The coating was made of melanin because the authors discovered that it could regulate the release of high-energy recoil electrons, which in turn prevented secondary ionisations and the production of reactive oxygen species (ROS). Three hours following injection, the bone marrow only contained 0.3% of the nanoparticles that had been delivered. It is unfortunate that the tumour spread was not documented. However, nude mice with A2058 human metastatic melanoma tumours on the flanks showed that the nanoparticles coated with melanin mitigated the effects of radioimmunotherapy (RIT). There was no discernible change in the antitumor effectiveness of these animals when treated with 1 mCi of 188Relabeled melanin-binding monoclonal antibody 6D2 alone or after pretreatment with nanoparticles coated with melanin and then administered the RIT. On the third day following treatment, the decrease in white blood cells was considerably less in the group that received nanoparticles coated with melanin.

It is hard to tell if this is correct because we didn't assess the concentration of nanoparticles in the tumour; it's also conceivable that there aren't that many. To determine whether the variation in white blood cell counts is due to radioprotection of the bone marrow, whether the nanoparticles are more effective antioxidants in the bone marrow than in the tumour, and, if so, how this difference in potency is achieved, further studies are definitely needed [42, 43]. However, no research has indicated if the anti-tumor efficacy is preserved when radiotherapy is paired with nanoceria;

studies have shown that nanoceria are more active antioxidants in normal tissue than in the tumour microenvironment. Remarkably, while intissue culture nanoceria shield a normal breast cancer cell line (CRL8798) from irradiation, they fail to do the same for a breast cancer cell line (MCF-7).

In this study, nanoceria were cerium oxide nanoparticles with varying valence states (Ce3+ and Ce4+) that were three to five nanometers in diameter. Radiation dose of 10 Gy was administered to 96-well plates containing CRL8798 and MCF-7 cells for the cell experiments. This caused a 40-50% reduction in cell viability in CRL8798 and MCF-7 cells when tested independently. Interestingly, CRL8798 cells showed nearly 100% protection when pretreated with 10 nM cerium oxide nanoparticles 24 hours before irradiation. In contrast, MCF-7 cells showed no benefit and died just as much as untreated cells. The exact mechanism causing the variation in protection was not known when this investigation was conducted. Nanoceria were found to be similarly taken up by squamous cancer cell line (SCL-1) and normal human dermal fibroblasts in a subsequent study. Both cell lines had aggregated nanoceria that were dispersed throughout the cytoplasm. The nanoparticles that were delivered had a size of 3-5 nm, whereas the ones that were observed had an intracellular size of 50 nm or larger. Most importantly, there was no discernible difference in uptake between the two cell lines; hence, the remarkably different radioprotection provided to normal breast cells compared to cancerous cells in the prior study cannot be explained by differences in intracellular concentration of nanoceria. Nanoceria can undergo a Fenton-like reaction, generating hydroxyl and peroxide radicals from hydrogen peroxide, as shown in a separate work by the same authors [44, 45]. In addition to their catalase and superoxide dismutase (SOD) activities, nanoceria also have this property, which allows them to convert hydrogen peroxide to water and oxygen [46–53]. The process of selective protection may involve balancing these three forms of action. Nanoceria may preferentially undergo a Fenton-like reaction rather than the other pathways, for instance, due to the elevated ROS levels found in cancer cells. In cancer cells, this would cause ROS levels to rise even higher, whereas in normal cells, it might promote catalase and superoxide dismutase activity, resulting in lower ROS levels. Because the nanoceria showed such exceptional selectivity in the pilot trial, more research is needed to understand the mechanism. We also need studies to see if this selection holds up in living organisms.

CONCLUSION

When it comes to cancer treatment and other nonmedically related radiation exposures, nanoparticles are a promising tool for selective radioprotection of normal tissue. They open up possibilities that small molecules and enzymes can't even begin to fathom due to their biopersistence and distinctive action mechanisms. Many studies have detailed the antioxidant capabilities of different nanomaterials and how they shield normal cells from radiation damage. Nevertheless, there is a dearth of literature on the topic of protecting healthy cells while leaving cancer cells unprotected, and even less on the topic of protecting healthy tissue when living organisms are being treated as tumours. Achieving selective protection in animal models will require much effort and perseverance. Even if some nanoparticles do manage to reach the region surrounding the tumour, their natural tendency is to gather in the RES organs. This means that the RES organs have the best system for selective accumulation in healthy tissues. Although this feature has only been used for imaging so far, we anticipate that it will be the most accessible region for using nanoparticles as radioprotectors. In addition to this use case, particles should be engineered to exhibit radioprotective activity that can be controlled by the local tissue microenvironment. This would allow them to exhibit distinct behaviour in normal tissue compared to diseased tissue. While accounts of this behaviour are intriguing, the underlying mechanisms are not. We can only hope that more research will shed light on these processes and ultimately lead to the development of more selective particles that can make it to the clinic. Novel nanoparticles may soon solve the unfulfilled clinical demand for selective radioprotection. We know that reactive oxygen species cause damage from ionising radiation, and we also know that antioxidants can mitigate some of these harmful effects. Free radicals, which are produced by ionising radiation, cause DNA damage, as previously stated. When free radicals produced by radiation react with biomolecules, the majority of the biological damage that radiation causes occurs. The frequency of DNA strand breaks may be decreased by substances that can scavenge free radicals. This means that radio-protectors can be agents that either stop free radicals from being formed or neutralise them by reacting with them, therefore preventing them from reacting with biomolecules. Since the other nanoparticles mentioned earlier have free radical scavenging activities, it is necessary to screen them for their potential radiation protection efficacy. Carbon, silver, gold, cerium oxide, etc., nanoparticles have been found to have radiation protection properties.

REFERENCES

1. Curtis A and Wilkinson C. Nanotechniques and approaches in biotechnology. Trends in Biotechnology. 2001;19:97-101.
2. Waren CW and Nie S. Quantum dot bioconjugates for ultra-sensitive nonisotopic detection. Science. 1998;281:2016-2018.
3. Vaseashta A and Dimova-Malinovska D. Nanostructured and nanoscale devices, sensors and detectors. Science and Technology of Advanced Materials. 2005;6:312-318.
4. Langer R. Drug delivery: drugs on target. Science. 2001;293:58- 59. 8. Roy K, Mao HQ, Huang SK and Leong KW. Oral gene delivery with Chitosan-DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. Nature Medicine. 1999;5:387- 391.
5. Sachlos E, Gotora D and Czernuszka JT. Collagen scaffolds reinforced with biomimetic composite nano-sized carbonatesubstituted hydroxyapatite crystals and shaped by rapid prototyping to contain internal microchannels. Tissue engineering. 2006;12:2479-2487
6. Karbownik M and Reiter RJ. Antioxidative Effects of Melatonin in Protection Against Cellular Damage Caused by Ionizing Radiation. Proceedings of the Society for Experimental Biology and Medicine. 2000; 225: 9-22.
7. United Nations Scientific Committee on the Effects of Atomic Radiation (2000). "Annex C: Exposures to the public from manmade sources of radiation". Sources and Effects of Ionizing Radiation. New York, NY: United Nations Publications. pp. 157–291. ISBN 978-92-1-142238-2.
8. Nair CK, Parida DK and Nomura T. Radioprotectors in radiotherapy. Journal of Radiation Research. 2001;42:21-37.
9. Gonzalez AB and Darby S. Risk of Cancer from Diagnostic X rays, Estimate for UK and 14 Other Countries, The Lancet. 2004;363:345-351.
10. Brenner DJ and Elliston CD. Estimated Radiation Risks Potentially Associated with Full Body CT Screening, Radiology. 2004;232:735-738.
11. Seed TM. Radiation protectants: current status and future prospects. Health Physics. 2005;89:531-45.
12. Hoffmann GR, Buccola J and Merz MS. Structure-activity analysis of the potentiation by aminothiols of the chromosome-damaging effect of bleomycin in G0 human lymphocytes. Environmental and Molecular Mutagenesis. 2001;37:117–127.
13. Weiss JF and Landauer MR. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. Toxicology. 2003;189:1-20.
14. Mettler FAJ and Voelz GL. Major radiation exposure : what to expect and how to respond. The New England Journal of Medicine. 2002;346:1554-1561.
15. Stone HB, Moulder JE, Coleman CN, Ang KK, Anscher MS, Barcellos-Hoff MH, et al. Models for evaluating agents intended for the prophylaxis, mitigation and treatment of radiation injuries. Radiation Research. 2004;162:711-728.
16. McBride WH, Chiang CS, Olson JL. Wang CC, Hong JH and Pajonk F. A sense of danger from radiation. Radiat. Res. 2004;162:1-19.
17. Kroto HW, Heath JP, O'Brien SC, Curl RF and Smalley RE. C60: Buckminsterfullerene. Nature. 1985;318:162-163.
18. Gharbi N, Pressac M, Hadchouel M, Szwarc H, Wilson H and Moussa F. Fullerene is an in vivo powerful antioxidant with no acute or sub-acute toxicity. Nano Letters 2005;5:2578-85.

19. Nielsen GD, Roursgaard M, Jensen KA, Poulsen SS and Larsen ST. In vivo biology and toxicology of fullerenes and their derivates. Basic & Clinical Pharmacology & Toxicology. 2008;103:197-208.

20. Krusic PJ, Wasserman E, Keizer PN, Morton JR and Preston KF. Science. 1991;254:1183-85.

21. Ali SS, Hardt JI, Quick KL, Kim-Han JS, Erlanger BF, Huang TT, et al. Free. Radic. Biol. Med. 2004;37:1191-1202

22. Guldi DM, Asmus KD. Activity of water-soluble fullerenes towards . radical OH-radicals and molecular oxygen. Radiation Physics and Chemistry. 1999;56:449-456.

23. Cheng F, Yang X, Zhu H, Sun J and Liu Y. Synthesis of oligoadducts of malonic acid C and their scavenging effects on hydroxyl radical. 60 Journal of Physics and Chemistry of Solids. 2000;61:1145-1148.

24. Sun T, Jia Z, Xu Z. Different hydroxyl radical scavenging activity of water-soluble â-alanine C60 adducts. Bioorganic & Medicinal Chemistry Letters. 2004;14:1779-1781.

25. Wang IC, Tai LA, Lee DD, Kanakamma PP, Shen CKF., Luh TY, et al. C60 and Water-Soluble Fullerene Derivatives as Antioxidants against Radical-Initiated Lipid Peroxidation. Journal of Medicinal Chemistry. 1999;42:4614-4620.

26. Alili, L., M. Sack, A. S. Karakoti, S. Teuber, K. Puschmann, S. M. Hirst et al. 2011. Combined cytotoxic and anti-invasive properties of redox-active nanoparticles in tumor–stroma interactions. Biomaterials 32:2918–2929.

27. Das, M., S. Patil, N. Bhargava, J. F. Kang, L. M. Riedel, S. Seal et al. 2007. Auto-catalytic ceria nanoparticles offer neuro- protection to adult rat spinal cord neurons. Biomaterials 28:1918–1925.

28. Dugan, L. L., D. M. Turetsky, C. Du, D. Lobner, M. Wheeler, C. R. Almli et al. 1997. Carboxyfullerenes as neuroprotective agents. Proceedings of the National Academy of Sciences of the United States of America 94:9434–9439.

29. Dugan, L. L., E. G. Lovett, K. L. Quick, J. Lotharius, T. T. Lin, and K. L. O'Malley. 2001. Fullerene-based antioxidants and neurodegenerative disorders. Parkinsonism and Related Disorders 7:243–246.

30. Hamm, B., T. Staks, M. Taupitz, R. Maibauer, A. Speidel, A. Huppertz et al. 1994. Contrast-enhanced MR imaging of liver and spleen: First experience in humans with a new superparamagnetic iron oxide. Journal of Magnetic Resonance Imaging 4:659–668.

31. Harisinghani, M. G., J. Barentsz, P. F. Hahn, W. M. Deserno, S. Tabatabaei, C. H. van de Kaa et al. 2003. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. New England Journal of Medicine 348:2491–2499.

32. Harrington, K. J., G. Rowlinson-Busza, K. N. Syrigos, P. S. Uster, R. M. Abra, and J. S. Stewart. 2000. Biodistribution and phar- macokinetics of 111In-DTPA-labelled pegylated liposomes in a human tumour xenograft model: Implications for novel targeting strategies. British Journal of Cancer 83:232–238.

33. Heckert, E. G., S. Seal, and W. T. Self. 2008. Fenton-like reaction catalyzed by the rare earth inner transition metal cerium. Environmental Science and Technology 42:5014–5019.

34. Hirst, S. M., A. S. Karakoti, R. D. Tyler, N. Sriranganathan, S. Seal, and C. M. Reilly. 2009. Anti-inflammatory properties of cerium oxide nanoparticles. Small 5:2848–2856.

35. Lucente-Schultz, R. M., V. C. Moore, A. D. Leonard, B. K. Price, D. V. Kosynkin, M. Lu et al. 2009. Antioxidant single-walled carbon nanotubes. Journal of the American Chemical Society 131:3934–3941.

36. Martin, R., C. Menchon, N. Apostolova, V. M. Victor, M. Alvaro, J. R. Herance et al. 2010. Nano-jewels in biology. Gold and platinum on diamond nanoparticles as antioxidant systems against cellular oxidative stress. ACS Nano 4:6957–6965.

37. Matsumura, Y., and H. Maeda. 1986. A new concept for macro-molecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Research 46:6387–6392.

38. McLachlan, S. J., M. R. Morris, M. A. Lucas, R. A. Fisco, M. N. Eakins, D. R. Fowler et al. 1994. Phase I clinical evaluation of a new iron oxide MR contrast agent. Journal of Magnetic Resonance Imaging 4:301–307.

39. Montet, X., R. Weissleder, and L. Josephson. 2006. Imaging pancreatic cancer with a peptide–nanoparticle conjugate targeted to normal pancreas. Bioconjugate Chemistry 17:905–911.

40. Murray, D., and W. H. McBride. 1996. Radioprotective agents. In: Kirk-OthmerEncyclopedia of Chemical Technology, edited by J. I. Kroschwitz, and M. Howe-Grant, 963–1006. New York: John Wiley & Sons.

41. Quick, K. L., S. S. Ali, R. Arch, C. Xiong, D. Wozniak, and L. L. Dugan. 2008. A carboxyfullerene SOD mimetic improves cognition and extends the lifespan of mice. Neurobiology of Aging 29:117–128.

42. Reimer, P., and T. Balzer. 2003. Ferucarbotran (Resovist): A new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: Properties, clinical development, and applications. European Radiology 13:1266–1276.

43. Riehemann, K., S. W. Schneider, T. A. Luger, B. Godin, M. Ferrari, and H. Fuchs. 2009. Nanomedicine—challenge and perspectives. Angewandte Chemie International Edition in English 48:872–897.

44. Ryan, J. L., S. Krishnan, B. Movsas, C. N. Coleman, B. Vikram, and S. S. Yoo. 2011. Decreasing the adverse effects of cancer therapy: An NCI workshop on the preclinical development of radiation injury mitigators/protectors. Radiation Research 176:688–691.

45. Schubert, D., R. Dargusch, J. Raitano, and S. W. Chan. 2006. Cerium and yttrium oxide nanoparticles are neuro-protective. Biochemical and Biophysical Research Communications 342:86–91.

46. Schweitzer, A. D., R. C. Howell, Z. Jiang, R. A. Bryan, G. Gerfen, C. C. Chen et al. 2009. Physico-chemical evaluation of rationally designed melanins as novel nature-inspired radioprotectors. PLoS One 4:e7229.

47. Schweitzer, A. D., E. Revskaya, P. Chu, V. Pazo, M. Friedman, J. D. Nosanchuk et al. 2010. Melanin-covered nanoparticles for protection of bone marrow during radiation therapy of cancer. International Journal of Radiation Oncology, Biology, Physics 78:1494–1502.

48. Seeney, T. R. 1979. A Survey of Compounds from the Antiradiation Drug Development Program of the U.S. Army Medical Research Development Command. Walter Reed Army Inst. of Research. U.S. Army Medical Research Development Command, Washington, D.C. Spencer, C. M., and K. L. Goa. 1995.

49. Amifostine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as a radioprotector and cytotoxic chemoprotector. Drugs 50:1001–1031.

50. Tarnuzzer, R. W., J. Colon, S. Patil, and S. Seal. 2005. Vacancy engineered ceria nanostructures for protection from radiation-induced cellular damage. Nano Letters 5:2573–2577.

51. Weiss, J. F., and M. R. Landauer. 2009. History and development of radiation-protective agents. International Journal of Radiation Biology 85:539–573.

52. Weissleder, R., D. D. Stark, B. L. Engelstad, B. R. Bacon, C. C. Compton, D. L. White et al. 1989. Superparamagnetic iron-oxide: Pharmacokinetics and toxicity. American Journal of Roentgenology 152:167–173.

53. Williams, J. P., S. L. Brown, G. E. Georges, M. Hauer-Jensen, R. P. Hill, A. K. Huser et al. 2010. Animal models for medical countermeasures to radiation exposure. Radiation Research 173:557–578.