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Harnessing the Power of Nanotechnology for Enhanced Radiation Therapy

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Abstract

Radiotherapy has emerged as one of the first lines of treatment in oncology. The past few decades have seen dramatic changes in the delivery of radiation therapy, with dose fractionation and treatment planning being the major focuses of research. Although effective, such empirical approaches are hardly optimal, and instances of patient mortality and tumor relapse are not rare. In this Perspective, we review the emerging technologies for optimization of radiosensitization, hypoxia modulation, and combinatorial therapeutic regimes for improved treatment outcomes in preclinical tumor models, with a focus on nanotechnology-mediated approaches. Such an approach is expected to open more productive avenues in the advancement of radiation therapy compared to simply modulating the radiation dose delivered to the tumor.

Graphical abstract

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Notes

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Since the first documented use of X-rays in treating lesions, radiation therapy (RT) has progressed to become one of the most effective and frequently applied curative and adjuvant treatment modalities in the clinic.¹ Employing high-energy X-ray or γ -ray, RT can kill cancer cells either by directly damaging the nuclear material or by generating oxygen-centric free radicals in the cells that can cause DNA damage. An estimated 60% of all cancer patients receive RT at some point during their treatment, either alone or in combination with chemotherapy or surgery. Despite phenomenal advances made in physical dose delivery of ionizing radiation in clinical settings, most of these approaches are highly empirical. The simplistic view that increasing the radiation dose would translate to increased therapeutic indices often results in suboptimal RT efficacy.² Moreover, innate or acquired radioresistance in a number of cancers (e.g., hypoxic tumors such as pancreatic cancer and glioblastoma) and off-target systemic cytotoxicity resulting from low radiotolerance of normal cells are well-documented challenges. Although combining radiation and chemotherapy has become a clinical standard in curative or palliative treatment regimens, concerns regarding the significantly increased off-target toxicity in most cases have severely undermined its usefulness.

In an effort to devise novel and more effective anticancer regimes, a rapidly growing community of researchers is applying the unique properties of nanomaterials to combat the unmet challenges posed by classical RT. The high surface area, stability, and facile tunability of nanomaterials make them ideal for transportation of chemotherapeutics, phototherapeutic agents, radiosensitizers, oxygen reservoirs, *etc.* across several physiological barriers. Prolonged blood circulation afforded by the use of nanocarriers, which exploit the enhanced permeability and retention (EPR) effect, enables higher accumulation of the drug at the tumor site. This approach has been investigated not only for improved chemotherapy but also for delivery of classical radiosensitizers to the tumor site.³ From employing high-Z elements (such as gold, gadolinium, iodine, bismuth, and rare earths) as radiosensitizers to concentrate higher doses of ionizing radiation at the target site, to modulating the hypoxic state of tumor tissue, as well as effectively combining multiple imaging and treatment modalities into a single system, nanomedicine presents several innovative strategies to improve therapeutic outcomes and, potentially, patient survival rates. In this Perspective, we

take a brief look at the emerging roles of nanotechnology in the rapidly evolving domain of modern/future radiation therapy.

Advances in Nanoparticle-Mediated Radiosensitization

A major advantage of RT lies in its noninvasive nature, which leads to less physiological and psychological burden being placed on the patients. However, collateral damage to healthy tissue resulting from its nonspecific nature means only limited doses can be administered, which, in turn, may result in tumor recurrence from a surviving population of radioresistant cells. Heavy elements with high photoelectric cross sections can produce a cascade of Auger/Compton electrons as well as scattered X-rays and photons when bombarded by ionizing radiation and, therefore, locally enhance the effective radiation dose (called the high-Z effect).⁴ Radiosensitization has thus become a classically applied adjunctive treatment, and dense inorganic nanoparticles are now widely employed as a means of improving the efficacy of single or fractionated radiation doses during cancer therapy. In addition, many nanomaterials demonstrate unique physicochemical properties, which, when combined with their radiosensitization capability, can open new opportunities for multimodal imaging and therapy, commonly called theranostics. For example, Au nanoparticles display excellent fluorescence, surface plasmon resonance, and photothermal properties, which, when combined with their X-ray accentuation, can result in an all-in-one multimodal nanotheranostic platform.⁵ Au nanoparticle-assisted RT has been around for about a decade. One of the pioneering studies reported the use of ~2 nm renal clearable Au nanoclusters for RT, with elevated accumulation (~7 mg Au/g) in tumor and ~86% one year survival in mice irradiated with 250 kVp X-ray.⁵ A plethora of studies involving Au nanoparticles with various shapes and sizes, targeting and therapeutic moieties, and delivery methods have since been reported.⁶ However, no clear consensus has been reached as to what can be considered an ideal nanoformulation, warranting substantial further research. Although gold remains the most extensively investigated nanomaterial for RT, other heavy metals, metal oxides, semimetals, lanthanides, and their complexes have also been documented in the literature for their radiosensitization properties.⁴

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Nanoparticle formulations of known radiosensitizers have also been shown to improve the delivery of such agents at the target site, owing to the EPR effect. For example, use of wortmannin, a potent inhibitor of DNA-dependent kinases and a well-known radiosensitizer, has been limited due to its poor solubility, low stability, and high toxicity. When encapsulated in a PEGylated polymeric core, wortmannin-containing nanoparticles were found to be more effective than either cisplatin *in vitro* or molecular wortmannin in murine tumor models.⁷ This strategy provides impetus for re-adoption of promising orphan radiosensitizer drugs such as wortmannin, which have been forgotten because of their unsuitable pharmacokinetic profiles.

Modulating Hypoxia for Enhanced Radiation Therapy

Radioresistance of hypoxic tumors is well-documented and has been a longstanding hurdle in maximizing RT outcomes in the clinic. Rapidly proliferating tumor cells and abnormal, malformed vasculature result in limited oxygen diffusion to the core of the tumor, which contributes to the reversal of radiation-induced DNA damage and, hence, suboptimal RT efficacy and, in many cases, tumor recurrence.⁸ In addition to RT, other treatment modalities such as chemo- and photodynamic therapies have been attenuated by hypoxic tumor microenvironments (characterized by low oxygen tension, low pH, low glucose concentration, and high reducibility), as well, necessitating the development of novel agents to combat this issue.⁹ Emerging data indicate that nanocarriers will play promising roles in modulating tumor hypoxia, and several strategies have been proposed to this end. An obvious strategy has been the delivery of hypoxia-responsive prodrugs such as tirapazamine, which can prevent reoxygenation in tumors and subsequent replication of any viable cells after RT.¹⁰

Improving tumor oxygenation has historically been employed as a means of overcoming hypoxia-related resistance to RT. The earliest attempts, which involved inhalation of 100% oxygen or carbogen, hyperthermia, and artificial blood substitutes carrying perfluorocarbon, were met with only partial or no clinical success.¹¹ Recent examples have adopted stimuli-responsive nanocarriers for more effective delivery of oxygen reservoirs such as perfluorohexane to trigger burst release of O₂ at the target site.^{12,13} A promising study documented the use of catalase enzyme-loaded bio-nanoreactors to improve local oxygenation by decomposing endogenous H₂O₂.¹⁴ In addition, normalization of tumor vasculature by several antiangiogenic agents can lead to enhanced blood perfusion and lower interstitial fluid pressure, which, when used in combination with RT, can help to overcome several limitations of chemoradiotherapy with enhanced efficacy and reduced toxicity.¹⁵ Although nanocarriers have been proposed for enhancing the therapeutic effects of antiangiogenic agents, their role in concomitant optimization of RT remains to be determined.

Multifunctional Nanomaterials for Combination Radiotherapy

One of the most exciting avenues of recent research involves administration of RT in combination with other therapeutic modalities. Monotherapeutic regimes seldom provide optimal treatment outcomes, which mandates synergistic action of two or more rationally selected therapeutic modalities. Chemoradiotherapy, with significantly better results than either chemotherapy or radiation therapy alone, has largely supplanted RT in the clinical management of a majority of locally advanced cancers. Sequential or concurrent administration of platinum-containing DNA cross-linking drugs (*e.g.*, cisplatin) with irradiation has been shown to sensitize tumors and to enhance RT outcomes.¹⁶ However, the ensuing side effects from injecting large doses of free drug have prompted the development of smart, efficacious nanocarriers for enhanced and/or targeted drug delivery. For example, liposomal formulations of doxorubicin in combination with RT have demonstrated enhanced efficacy in patients with non-small cell lung cancer and early stage Hodgkin's disease when compared to patients receiving monotherapies.^{17,18} In addition, several clinical trials are

currently evaluating the feasibility of combining novel nanoparticle formulations of drugs (*e.g.*, paclitaxel, cisplatin, *etc.*) with RT in a wide variety of cancer types.¹⁹

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In order to optimize combination therapy of solid tumors, next-generation nanomedicines are designed to co-deliver multiple drugs, different therapeutic agents, and even imaging probes all in the same nanoplatform, to enable enhanced ratiometric drug loading, bioresponsive/tunable drug release profiles, synergistic treatment efficacies, and image-guided therapy. For example, Fan *et al.* reported a cisplatin-loaded, upconversion nanoparticle-based rattle-type nanoplatform for synergistic chemoradiotherapy and magnetic/luminescent dual-modal imaging.²⁰

Moving beyond drug delivery, nanoparticles are now being explored for their intrinsic anticancer activities. In an intriguing study published in the May issue of *ACS Nano*, Chen and co-workers demonstrated the synergistic radiochemotherapeutic prowess of novel core-shell nanocomposites in treating melanoma xenografts, combining the radiosensitization of Au nanorods with the apparent antitumor activity of Se nanoparticles.²¹ In addition to overcoming resistance developed by tumors to traditional drugs, vasculature-targeting Au–Se nanoparticles also alleviate toxicity concerns posed by traditional chemoradiotherapy.

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Another combinatorial approach gaining much traction is simultaneous radiation and phototherapy for synergistic ablation of tumors. Phototherapy generally involves two paradigms, photothermal therapy (PTT) and photodynamic therapy (PDT), both of which have extensively been shown to enhance RT in curbing tumor growth, prolonging post-therapy survival, and reducing local and systemic side effects.^{22,23} Differences in the mechanisms and sites of action between phototherapeutic modalities and RT promise mutual benefits to both, thereby generating strong synergistic effects. Extensive *in vitro* and *in vivo* preclinical studies, as well as randomized clinical trials, have established the significant benefits of hyperthermia to RT in improving treatment outcomes.²² Whereas RT overcomes the shortcomings of PTT in treating deep-seated tumors, the role of hyperthermia in enhancing RT can be attributed to enhanced thermal susceptibility of radioresistant S-phase and hypoxic cells, increased blood flow, and thus improved tissue oxygenation resulting from localized heating, and effective suppression of repair in nonlethally damaged cells.²⁴

In an early report, Diagaradjane *et al.* utilized Au nanoshells for combined RT/PTT in colorectal cancer with superior performance over monotherapies.²⁵ Several studies have since reported the use of more effective or less costly nanoformulations composed of high atomic weight nanomaterials alone or in conjunction with nanoparticulate photosensitizers for enhanced combination therapy of tumors.^{24,26–28} Despite extensive advances in combined RT/PTT in the preclinical setting, logistical problems associated with the

simultaneous delivery of heat and radiation, nonspecific accumulation of the nanomaterials, and difficulty in photoirradiation of deep-seated tumors, *etc.*, have impeded the clinical translation of this promising paradigm. To circumvent the latter, Li and coworkers have reported ultrasmall Bi nanoparticles that have the ability to absorb both the ionizing and second near-infrared (NIR-II) window laser irradiations, for effective and synergistic treatment of tumors.²⁹

Contrary to RT and chemotherapy, which act by immunosuppression, PDT works by activating the immune system and can be an excellent choice for synergistic coupling with RT. In addition, RT acts at the proximity to the cell nuclei and is suitable for treatment of larger lesions. Photodynamic therapy on the other hand, works best around the cell membrane, and is desirable for smaller lesions, further validating the complementary nature of RT and PDT.^{4,23} Although clinical high-energy radiation is not suitable for the activation of most traditional photosensitizers, seminal work by Chen and Zhang in 2006 employed scintillator nanoparticles conjugated to photosensitizer molecules to act as down-conversion mediators.³⁰ X-ray excited luminescence from the nanoscintillator could internally activate the photosensitizer to generate singlet oxygen species for subsequent PDT. The simplicity of such a design fueled intense research as the unlimited tissue penetration of radiation and efficacy and safety of PDT offered conceivably enhanced therapeutic outcomes. Further, the use of a single excitation source promised more straightforward clinical application in terms of hardware design and logistics. Following this strategy, a number of sophisticated studies have been proposed in the past decade to overcome certain key disadvantages of this additive combination: destruction of the nanoscintillator and photosensitizer upon exposure to ionizing radiation and consequent toxicity concerns, as well as strong oxygen dependency of both RT and PDT.^{31–34} In an elegant study, synchronous radiotherapy and ionizing radiation-induced deep PDT were achieved by integrating a nanoscintillator and a semiconductor photosensitizer, with excellent photostability and diminished oxygen dependence for greatly enhanced therapeutic efficacy.³¹

CONCLUSIONS AND OUTLOOK

Decades of research and empirical improvements have made RT one of the primary treatment modalities for many cancer types, despite the advances made in other therapeutic techniques. Continued progress in treatment planning systems, as well as dose-delivery logistics, has enabled more precise delivery of radiation doses to the target tissue (in the case of three-dimensional conformal and intensity-modulated RT) or greater dose fractions to be delivered over reduced treatment times (as in stereotactic body RT). As one of the most widely used treatment strategies, RT is naturally subjected to intensive research to improve its therapeutic outcomes. With slow infiltration of nanotechnology into the clinic, the field of cancer nanomedicine is just beginning to flourish. Novel nanomaterials and newly identified applications of well-established ones are expected to revolutionize classical areas of RT such as radiosensitization and radioprotection. Importantly, the use of multifunctional nanoparticles in RT is attractive as they can combine different imaging and therapeutic modalities for image-guided drug delivery and release and minimally invasive therapy.

Despite a plethora of preclinical studies, nanoparticle-mediated combination RT/phototherapy has not yet been translated in the clinic. A single phase II trial (NCT02850419) involving thermally sensitive liposomal doxorubicin formulation for thermoradiotherapy of breast cancer has been reported to date, poised to begin in the near future. While hyperthermia applications of two Au nanoformulations have been FDA approved for clinical trials,⁴ no nanoscale photodynamic or radiosensitization agents have made the cut, indicating a long road ahead for nanomaterial-mediated radiation therapy. However, considering the frequency of innovative studies, the tremendous investment from various funding agencies, and a strong push to understand the essential principles involved in these paradigms, the burgeoning field of nanomedicine holds great promise for future precision cancer therapy.

As the field progresses, several key points need attention. First, there is a pressing need for rationally designed nanoformulations that exhibit optimal tumor-homing and intratumor distribution. Improved tumor penetration by such nanoformulations can enhance RT outcomes, especially when combined with hypoxia-responsive therapies. The complex tumor microenvironment undergoes dynamic interactions with administered nanoparticles and RT, which can drastically influence treatment outcomes and, thus, warrant careful consideration during therapy planning. Second, a paucity of data on the long-term *in vivo* behavior and toxicity profiles of nanoparticles has severely impeded the transition of even well-established nanoformulations from preclinical to clinical settings. In this regard, molecular imaging can provide useful information about the spatiotemporal distribution and dose profiles of nanomaterials, help evaluate therapeutic responses, and predict therapy outcomes. Despite sophisticated designs and excellent preclinical performance, most nanoparticles employed for RT to date demonstrate suboptimal pharmacokinetics *in vivo*, leading to grave toxicity concerns and even rejection of such “fantastical studies” by many in the medical community. Although innovative technologies are important for moving the field forward, in-depth evaluation of their interactions with tissues and cells is certainly warranted.

Considering the frequency of innovative studies, the tremendous investment from various funding agencies, and a strong push to understand the essential principles involved in these paradigms, the burgeoning field of nanomedicine holds great promise for future precision cancer therapy.

Third, nanotechnology provides a promising platform to bridge the gap between the newly emerging targeted therapies and traditional RT. For example, immunotherapy has generated much excitement in the medical community owing to its exemplary results in melanoma patients.³⁵ Nanoparticle-based radiosensitizers designed to deliver alternative payloads such as immune adjuvants as well as angiostatic drugs and antibodies are interesting avenues to explore. Finally, concerted efforts on the part of scientists and regulatory authorities are required to expedite the translation of promising, clinically beneficial nanomaterials from bench to bedside. Continued support and investment from governments and other funding agencies is needed for cancer nanotechnology-related research before we can harness the full power of this exciting technology and reap its fruit for future precision cancer therapy in the clinic to benefit millions of patients.

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