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Physics Update

The future of nanotechnology in radiation therapy

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Nanotechnology is an exciting and rapidly developing field with ramifications in engineering, material science, biology and medicine. The term nanomedicine was coined by the National Institutes of Health to recognize the fast-growing field and its potential to fundamentally change the way diseases are diagnosed, treated and prevented.

Nanomaterials are engineered to have one or multiple physical properties, such as fluorescence and magnetism, which are enhanced and are often drastically different from bulk material of the same chemical composition. Moreover, their large surface areas are highly modifiable to carry different electrical charges, water solubilities, biocompatibilities and most importantly, affinities to certain cells and physiological environments. The infinite combinations of nanomaterial sizes, morphology, physical and chemical properties, and surface modifications provide tremendous research opportunities for a wide range of biomedical topics. Naturally, nanotechnology has found a home in cancer research.

While general cancer imaging is the inseparable twin of cancer therapy, there has been a direct infiltration of nanotechnology into radiation therapy. Two eternal topics in radiation therapy, radiosensitization and radioprotection, have exemplified the use of nanotechnology. High atomic number nanoparticles can increase the attenuation and local radiation dose from X-rays. Increased tumor cell killing was observed with the uptake of Au nanoparticles and kV X-rays. Due to the diminishing importance of photoelectric reaction in the MV X-ray range, the potential to use gold nanoparticles for human radiosensitization has been seriously challenged. Nonetheless, a notion has emerged that the intratumoral distribution of Au nanoparticles may be highly heterogeneous, creating much greater local radiation dose where the particles aggregate and increasing tumor and tumor supporting tissue destruction1. The notion needs substantiating evidence from future cell and animal studies, but the idea of high atomic number nanoparticles for radiosensitization remains active.

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Radiation damage to cells is predominantly through free radicals generated from the ionization process. Several types of nanomaterials, including CeO_2 nanoparticles, have been developed to reduce the normal damage from free radicals. The cerium atom can exist in either the +3 (fully reduced) or +4 (fully oxidized) state. In its oxidative form, CeO_2 also exhibits oxygen vacancies, or defects, in the lattice structure, through loss of oxygen and/or its electrons, alternating between CeO_2 and CeO_{2-x} during redox reactions. The change in cerium valence during a redox event subsequently alters the structure of the oxide lattice, possibly creating additional oxygen vacancies by lattice expansion. This electron translation within the lattice provides reduced power for free radical scavenging. After the scavenging event, the original lattice structure may be regenerated by releasing H_2O while the cerium atom returns to the +3 state. Colon et al. showed that CeO_2 nanoparticles, which were well tolerated by study animals, effectively protected mice from 20-Gy thoracic irradiation2. Although there is evidence that normal tissue is protected by CeO_2 nanoparticles, its mechanism needs to be better understood and methods to improve the specificity developed.

Nanoparticles can be fabricated to directly deliver the radiation dose to the tumor, a technology called nanobrachytherapy3. The idea of delivering radionuclides to the tumor for treatment has been well established

in radioimmunology, but fabricating radionuclides into nanomaterials can add properties, such as magnetism for MR imaging. Success of nanobrachytherapy relies on tumor targeting specificity, a paramount topic in almost all cancer nanotechnological research areas. Both passive tumor targeting methods, e.g., enhanced permeation and retention effects, and active targeting methods, e.g., using antibodies and peptides binding with tumor cell receptors, have been explored with varying degrees of success. Most likely, nanobrachytherapy will benefit from the greater collective effort.

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Beyond these classical radiation therapy topics, radiation also can be seen as a precise way of delivering a quantitative stimulus to tissue for secondary therapy and imaging with the assistance of nanomaterials. One such example is simultaneous photodynamic therapy with radiation therapy. Photodynamic therapy kills cells by mechanisms very different from radiation therapy and can be used to overcome radioresistance. A quantum dot-photosensitizer conjugate was synthesized to utilize radiation energy from therapeutic X-ray for photodynamic therapy. Using quantum dots as the energy medium, Yang et al. demonstrated the energy transfer from MV to photosensitizers and subsequent singlet-oxygen-induced cell death4. Because of the highly quantitative nature of radiation dose, in theory, photodynamic therapy can be switched on at locations exposed to a threshold radiation isodose that is made conforming to the tumor by methods such as intensity modulated radiotherapy. Another creative example is by exploiting radiation-induced immunological response. Hariri et al. showed that moderate radiation doses can upregulate vascular endothelium cell surface protein expression that bonded specifically to FePt nanoparticles decorated with HVGGSSV peptides5. This interesting pathway opens opportunities for radiation therapy-induced drug delivery, treatment response imaging and *in vivo* 3-D dosimetry.

Additionally, the future breakthrough in adopting nanomaterials for more effective radiation therapy can be an interactive one. A recent trend in nanotechnological research is to engineer the nanomaterials so it is only activated by specific environmental factors, such as the heat, pH value and magnetic field. The ability to do so with X-ray irradiation would add another dimension to the research. An early example has been shown by Beaulac et al. in that the magnetism of doped colloidal quantum dots can be controlled by light6, providing a way to “see” where we treat in a MR-guided radiation therapy setting.

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Overall, it is fair to say that the nanotechnological infiltration into radiation therapy is still beginning with many aspects remaining to be discovered. The next major breakthrough could come from one of the classical radiotherapy topics in radiosensitization, protection or dosimetry; or as material media to bridge X-ray energy with a secondary physical, chemical or biological process for cancer treatment. As scientists and clinicians in radiation therapy, it is important to keep an open mind. The future of radiation therapy may very well reside in the future of nanotechnology.

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