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Review

Nanoparticles for radiooncology: Mission, vision, challenges

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ABSTRACT

Cancer is one of the leading non-communicable diseases with highest mortality rates worldwide. About half of all cancer patients receive radiation treatment in the course of their disease. However, treatment outcome and curative potential of radiotherapy is often impeded by genetically and/or environmentally driven mechanisms of tumor radioresistance and normal tissue radiotoxicity. While nanomedicine-based tools for imaging, dosimetry and treatment are potential keys to the improvement of therapeutic efficacy and reducing side effects, radiotherapy is an established technique to eradicate the tumor cells. In order to progress the introduction of nanoparticles in radiooncology, due to the highly interdisciplinary nature, expertise in chemistry, radiobiology and translational research is needed. In this report recent insights and promising policies to design nanotechnology-based therapeutics for tumor radiosensitization will be discussed. An attempt is made to cover the entire field from preclinical development to clinical studies. Hence, this report illustrates (1) the radio- and tumor-biological rationales for combining nanostructures with radiotherapy, (2) tumor-site targeting strategies and mechanisms of cellular uptake, (3) biological response hypotheses for new nanomaterials of interest, and (4) challenges to translate the research findings into clinical trials.

1. Introduction

According to the world health organization (WHO), the number of cancer-related mortalities per year is projected to increase by 45% from 2007 to 2030, influenced in part by an increasing global aging population. In today's society, the costs of cancer care are enormous, where the EU spends annually ~126 billion €. More than 14 million new cases and >8 million cancer deaths were reported worldwide during 2012–2013, with an elevating trend described in GLOBOCAN by the International Agency for Research on Cancer (IARC) and the Institute for Health Metrics and Evaluation (IHME) [1,2]. These data underline the urgent need for a re-evaluation and prioritization of new approaches to complement and improve current diagnostic tools and treatment methods. The latter

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comprises the three main pillars of cancer treatment, namely surgery, radio- and chemotherapy, which were over the past decade extended by a range of novel chemotherapeutic as well as individually applicable targeted therapeutics and immunotherapies. Patients with specific malignant diseases clearly benefit from the reasonable progress in surgical and chemotherapeutic treatment. However, only marginal improvement in overall clinical management of cancers patients could be achieved, with some malignant diseases such as pancreatic cancers and glioblastomas, as well as most advanced stage cancers, remaining an unsolved therapeutic challenge. Here, the most prominent limitations of currently available treatment options such as dose-limiting toxicity, lack of specificity, selectivity, bioavailability of drug candidates or local distribution, and morbidity become particularly apparent. Novel strategies that are generally applicable, have high (local) efficacy and are cost-efficient, are of utmost urgency [3]. A great hope lies in the field of nanomedicine, where nanoparticles (NPs) can be specifically designed using advanced engineering tools to treat and visualize tumors. Several NP based fomulations are undergoing clinical trials, or are even already used in clinics [4,5]. Most applications however merely utilize NPs as drug delivery vehicles or as mediators in physical anticancer methods, such as heating of tumor cells. In particular the delivery vehicle aspect has been critically discussed recently [6]. These methods suffer from several drawbacks, such as the need for advanced NP surface chemistry, specialized equipment, lack of specificity, low efficiency in drug release rates, and undesired NP toxicity [7–11]. For imaging applications, NPs either contain intrinsic contrast (*e.g.* FeO_x cores for magnetic resonance imaging (MRI)), or are further functionalized through chemical means (*e.g.* fluorescence or radiolabeled probes) [12]. These functionalities enable follow-up of the NPs' location after administration, but do not give any direct information on the ongoing therapy.

Photodynamic therapy (PDT) consists of light, photosensitizer and oxygen during treatment. The mechanism of PDT involves activating photosensitizers *via* certain wavelength of light followed by emission (recombination). The whole excitation-emission process is accompanied with the energy release that is transferred to the near surface oxygen generating ROS (singlet oxygen, free radicals and/or superoxide) [13]. The chemical reactions that take place during PDT are (1) the direct interaction of excited photosensitizers with the cell membrane or the cellular components transferring H atom to form potentially hazardous radicals and (2) direct energy transfer from the excited photosensitizers to surface oxygen generating singlet oxygen ($^1O_2$) and/or highly oxidizing superoxide [13]. Hence, for the progress in cancer therapy using PDT technology, the development of new light sensitive photosensitizers will be of great interest. During treatment, these efficient photosensitizers are expected to be cleared from the body faster and absorb light at higher wavelengths leading to a limited period of photosensitivity in the targeted area [14–19]. Designing such sensitizers (altered or mixed to target specific cell abnormalities) targeting various organs and parts of the cell such as membrane and lysosomes are very promising in treatment of tumors. Although PDT is an effective technique to treat certain types of cancers, in particular those located at surfaces and/or successible via orifice of the body, the technique still has serious drawbacks for the treatment of deep tissue tumors. e.g. due to the penetration limits of the available light source(s). Also, effective photosenistizers with reduced duration of light irradiation have intense and prolonged chemical reactions post treatment [20]. Nonetheless, a lot can be learned from recent developments and use of nanoparticles in PDT for putative combination with radiotherapy, i.e. using X-rays as energy source to activate the PDT-underlying process (e.g. [472]). Hence, in the future, photodynamic therapy (PDT) in combination with surgery and radiotherapy could be uniquely tailored to treat cancers [21]. The treatment includes the development of new photosensitizers, using optimal photodynamic therapy protocols (light fraction and/or drug dose) [22,23]. Furthermore, the clinical trials involving selective and friendly sensitizers with low energetic light irradiation may improve the photodynamic therapy technique in cancer treatment [24,25].

The use of NPs in the context of radiotherapy is a particular issue that has been challenging in the past. Radiotherapy as one of the key modalities to treat solid cancers and is the major treatment option beyond surgery with high curative potential. Today, about 50–60% of the cancer patients receive radiotherapy, most frequently in entity-specific combinatorial radio/chemotherapeutic approaches [26,27]. The success rate and outcome of patients is still limited by normal tissue toxicities and the development of individual, highly variable intrinsic as well as microenvironmentally-driven tumor therapy resistances that require improvement and optimization of the current treatment policies [27–31]. Here development of novel strategies and types of nanoparticles and -materials, in particular to ameliorate the cancer-specific efficacy of radiotherapy would be highly helpful. It is recognized that some materials might be considered as dosimetric *in-vivo* nanosensors to monitor therapeutic levels of ionizing radiation as recently shown for C12 TAB-templated gold NPs exhibiting unique spectral profiles under ionizing radiation [3]. However, in this report focus will be given rather describing a vision of NPs for radiosensitization based on the cellular irradiation effects and tumor biological rationales, as depicted in the following. Therapeutic challenges will be highlighted and some specific examples of interest are given.

2. Cellular irradiation effects and tumor biological rationales

Radiotherapy may eradicate cancer cells through a set of physical and chemical changes induced in the tumor tissues *via* transmitted energy. Many different types of ionizing radiation have been employed for medical diagnostic and therapeutic applications including photons (X-rays, gamma rays), leptons (electrons), hadrons (negative pi-mesons, neutrons, protons) and heavier ions (carbon, silicon, neon, helium). The major considerations for selections of the certain type of ionizing radiation for medical use include its controllability within an atomic site, inherent pattern of ionizing density defined by the linear energy transfer (LET), and relative biological effectiveness (RBE), attributed to the relative biological effects per unit energy [32]. Up to date, X-rays (photons) remain the most common type of radiation therapy due to its low production cost [33]. State-of-the-art photon radiotherapy is based on continuous technological progress over the past decades that led to an advanced 3D conformal treatment, and includes the use of intensity-modulated radiation therapy (IMRT) techniques with in-room image guidance (image-guided radiation therapy). Particle therapy with protons or heavier ions such as carbons has the potential for higher dose conformity compared with photon beams, due to a reverse depth dose profile, *i.e.* particle beams can be directed more precisely as they deposit most of their energy over a narrow range (Bragg peak) [34–39]. The energy of the beam defines the depth of the Bragg peak in tissue and can be modulated to achieve maximum ionization within the tumor site and spare organs of risk to minimize normal tissue injury. Although high equipment and facility costs are the major obstacle for wider applications, proton and carbon ion therapy has been shown to be an efficient treatment modalities for different types of malignancies, including head and neck squamous cell carcinoma (HNSCC), prostate, brain, and pediatric cancers [40–42]. More details on the technical improvements in photon and particle therapy have been discussed in a recent report highlighting the efforts in biology-