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Review

Cancer nanotheranostics: Strategies, promises and impediments

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ABSTRACT

Cancer has remained one of the most indomitable conundrums for scientists over centuries due to its multifarious etiology. While improved therapeutic and diagnostic approaches have commendably augmented the rate of survival of cancer patients, a holistic riddance from the ailment is still implausible. Hence, further explorations to scout for novel strategies of cancer therapy and diagnosis are necessary. Theranostics (amalgamation of therapy and diagnostics) has emerged as one of the *avant-garde* strategies, which provides a two-pronged advantage in cancer management. This integrative approach has found immense relevance in light of nanotechnology. Nanoparticles can be customized (loaded with a mélange of therapeutic drugs and diagnostic probes) to develop theranostic properties, thereby constructing nanotheranostic agents. These nano-composites are lucrative tools for cancer cell obliteration and simultaneous monitoring of the drug action, and can also be tailored for targeted drug delivery. Nanotheranostic agents have emerged as a prudent ploy for synchronized cancer intervention and detection of the 'route and reach' of the drugs. In this review, we discuss the diversified state-of-the-art facets of theranostic nanoparticles, including various nanoparticle-based platforms as well as the plethora of reported therapeutic drugs, aptamers, markers and diagnostic molecules that have found use in the precincts of nanotheranostics.

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Contents

Abbreviations: 4D CRT, four-dimensional conformal radiotherapy; AFP, α-fetoprotein; AuNB, gold nanobeacons; AuNC, gold nanocluster; AuNP, gold nanoparticle; AuNR, gold nanorod; AuNS, gold nanostar; B2M, β2-microglobulin; BSA, bovine serum albumin; CEA, carcinoembryonic antigen; CLSM, confocal scanning microscopy; CPT, camptothecin; CT, computed tomography; DBCO, dibenzocyclooctyl; Dox, doxorubicin; EPI, epirubicin; EPR, enhanced permeability and retention; FLIM, fluorescence lifetime imaging microscopy; FR, folate receptor; GO, graphene oxide; HCG, human chorionic gonadotropin; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; IONP, iron oxide nanoparticle; LOG, low-oxygen graphene; MG-Nf, magnetic-gold nanoflower; MNP, magnetic nanoparticle; MRI, magnetic resonance imaging; MS flakes, molybdenum disulphide flakes; MSN, mesoporous silica nanoparticle; NGO, nano graphene oxide; NIR, near-infrared; NP, nanoparticle; OCT, Moptical coherence tomography microscopy; PAI, photoacoustic imaging; PAT, photoacoustic tomography; Pc, phthalocyanine; PCL, paclitaxel; PDT, photodynamic therapy; PEG, polyethyl glycol; PET, positron-emission tomography; PFP, *n*-perfluoropentane; PLP, porphylipoprotein; PTT, photothermal therapy; PZP, pregnancy-zone protein; RIS, CRNA-induced silencing complex; ROS, reactive oxygen species; SERRS, surface-enhanced resonance Raman spectroscopy; SERS, surface-enhanced Raman spectroscopy; SiNc, silicon naphthalocyanine; SiNP, silica nanoparticle; SPECT, single photon emission computed tomography; SPION, superparamagnetic iron oxide nanoparticle; SWCNT, single-walled carbon nanotube; TEM, transmission electron microscopy; TPL, two-photon luminescence; UCLI, upconversion luminescent imaging; UCNP, upconversion nanoparticle.

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1. Cancer and its ominous subsistence

Despite decades of research, cancer remains at large as a colossal global threat. Characterized by uncontrolled cell growth capable of intruding any part of the body, cancer is in fact a conglomeration of multiple neoplastic diseases that might be triggered by a plethora of factors – both endogenous and exogenous [1]. Currently, it is the second leading cause of mortality in the United States, and is predicted to surpass cardiac diseases to be the paramount cause of death in the coming years [2,3]. The statistics of cancer-associated mortality around the world are alarming [4]. While pulmonary cancer (affecting lung, bronchus and trachea) is the predominant cause of worldwide cancer-related deaths (~1.1 million in 2012) in men, breast cancer claims maximum lives in women (~0.52 million in 2012) [5]. In 2016, the estimated number of cancer-related deaths in USA is a staggering 595,690, while the projected number of incidences is 1,685,210 [6]. About 13.59 million cancer deaths are predicted in the European Union alone in 2016 [7]. At the global arena, from 16.6 million in 2015, the number of cancer patients is speculated to reach 21 million by 2030 [3,8]. Such overwhelming census is not only implicative of the humongous toll on human health, but also underlines the massive financial burden cancer incurs *via* the costs of treatment and palliative care. According to a 2015 report published in Forbes magazine, the global cancer drug market touched the US $100 billion mark in 2015, and is predicted to reach US $147 billion by 2018 [9]. These appalling numbers necessitate further research to explore better, safer and more effective therapeutic and diagnostic strategies.

2. Strategies of intervention and diagnosis of cancer

Recent decades stand testimony to a deluge of novel and advanced strategies that have emerged as a crusade to avert the number of cancer deaths. The conventional strategies commonly employed to combat cancer include surgery, chemotherapy, radiotherapy, stem cell transplant therapy, immunotherapy, and various targeted therapies [10]. Surgical interventions have always been a popular mode of cancer treatment. Several approaches such as thoracoscopic, laparoscopic, endoscopic, laser and cryo-based surgeries have found success in controlling chest, abdomen and colon cancers, as well as cancers of the skin, liver, larynx and cervix [11]. However, frequent post-surgery relapse often necessitates adoption of adjuvant therapies, such as chemotherapy and radiotherapy (or combination of both) [12]. In fact, chemotherapy has been single-handedly successful in controlling multiple types of cancer, including myeloma, lymphoma, sarcoma, leukemia, breast cancer, lung cancer etc. by administration of drugs such as corticosteroids (dexamethasone, prednisone, methylprednisolon etc.), anti-tumor antibiotics (epirubicin, daunorubicin, mitomycin C), alkylating agents (busulfan, mechlorethamine, streptozocin), topoisomerase inhibitors (topotecan, teniposide etc.), antimetabolites (5-fluorouracil, floxuridine, etc.) and various mitotic inhibitors (taxanes, epothilones, etc.) [13]. Recent advancements in radiotherapy, such as image guided radiotherapy (IGRT), four-dimensional conformal radiotherapy (4D CRT) and intensity modulated radiotherapy (IMRT), bolster their accomplishments in the intervention of the progression of prostate, breast, and head and neck cancers [14].

In recent years, various prominent immunotherapeutic cancer drugs have emerged. These drugs modulate the facets of the immune system that are involved in malignancy (such as PD-1, CTLA-4, CD160, CD244, VISTA, BTLA etc.) [15]. Anti-PD-1 antibodies like pembrolizumab, nivolumab and pidilizumab are used to treat renal cell carcinoma, head and neck carcinoma, lymphoma and melanoma [16]. Another recent development in the field of cancer therapy is the use of the RNA interference (RNAi) approach, which is used to target cellular proteins responsible for neoplasticity in order to inhibit malignancy. For example, small interfering RNA (siRNA) is used to treat chronic and acute myeloid leukemia by blocking mRNA translation or by targeting aberrant proteins like BCR-ABL fusion protein [17]. Micro RNAs (miRNAs) are also used for prognosis and therapy in cancer [18]. For instance, antisense miRNAs antagomiRs are used to disrupt the RNA-induced silencing complex (RISC) [19]. In another approach, miRNA sponges are used to silence miR-9, which in turn inhibits metastasis [20].

In spite of the considerable progress in developing cancer therapeutics, their deleterious side effects are of paramount concern. Chemotherapy drugs, for instance, are known to cause a conglomeration of conditions, including osteoporosis, infertility, premature ovarian failure, typhlitis, herpesviridae infections, hair loss, diarrhea and constipation [21–26]. Like chemotherapy, radiotherapy too has its share of adverse effects. These include heart diseases, nausea, gastrointestinal lesions, gastric pain and a host of other conditions [27–29]. Although RNAi-based therapies do not face these problems, siRNA/miRNA are susceptible to various nucleases, which reduce their stability and functional efficiency [30]. Also, the negatively charged backbones of these oligonucleotides pose hurdles in their effective delivery to their cellular targets [31]. The complex and diverse cross-talks amongst pathways associated with the *modus operandi* of cancer pose a major challenge in devising a blueprint for therapeutic intervention. Targeting a particular factor necessitates detecting the same in the first place. Thus, it becomes imperative to have an effective diagnosis approach which can eventually enable the proposition of the necessary therapeutic regimen.

Over decades, researchers have developed strategies for effective diagnosis of tumors. For example, a computed tomography (CT) scan of the body is used to monitor abnormal growth and the presence of any tumor, as well as the reappearance of the tumors and the stage of their malignancies, in order to provide guidelines for biopsy and surgical options [32]. Other systems used for diagnosis are ultrasound, x-ray, magnetic resonance imaging (MRI), nuclear scan etc. and most importantly biopsy (with the collection of a tissue or fluid sample, *via* needle, endoscope or surgery) [33]. Different kinds of tumor markers are in use to diagnose various cancers, such as uPA/PAI1 for breast cancer [34], carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) for the diagnosis of cholangiocarcinoma [35], OCAA/OCAA-1, human chorionic gonadotropin, (HCG), α-fetoprotein

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