Comment

Black phosphorus-based nano-drug delivery systems for cancer treatment: Opportunities and challenges

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The numbers of research studies investigating black phosphorus (BP)-based nano-drug delivery systems and their potential applications are rapidly growing because of the unique properties of BP (such as a layer-dependent bandgap, moderate carrier mobility, high capacity of drug loading, intrinsic photothermal and photoacoustic properties, good biocompatibility, etc.). They are highly suitable for phototherapy (photothermal therapy and photodynamic therapy), drug delivery, bioimaging and theranostics [1]. In the present report, the opportunities for BP nanomaterial-based drug delivery systems are highlighted. Furthermore, challenges in functional modification, stabilization and long-term biosafety of BP nanoparticles are addressed. Finally, the future perspectives for applications of BP-based nano-drug delivery systems (such as immunotherapy, multi-modal combination therapy, biosensing, bio-imaging and theranostics) for precision diagnosis and treatment of tumors are anticipated. With its broad spectrum of light absorption and excellent photothermal conversion efficiency, BP nanomaterials have tremendous potential as applications in the biomedical field [2]. They are effective at absorbing near-infrared light at wavelength of approximate 800 nm and generating photo-thermal effect, thus are excellent photothermal reagents for killing tumors. Photothermal therapy (PTT) using BP nanodrug delivery systems exhibits a low invasion effect with high treatment efficiency. In addition, BP is effective in generating singlet oxygen and other reactive oxygen species under near infrared light at wavelength of 660 nm, which can be used as photosensitizer for photodynamic therapy (PDT). This offers therapeutic benefits for skin cancer, nasopharyngeal carcinoma, breast cancer, cervical cancer and other superficial tumors. Furthermore, BP offers high drug loading capacity for drugs or other agents due to its high specific surface area [3]. Partially-oxidized phosphoric acid endows BP with a negative surface charge, facilitating the delivery of positively charged chemotherapy or genetic drugs to tumor sites through electrostatic interactions [4]. Mei et al. first fabricated a novel theranostic delivery platform using BP nanosheets, which demonstrated that “macropinocytosis (Rab34-labeled)→late endosomes (Rab7-labeled)→lysosomes” could be a novel endocytotic pathway in the turnover of BP nanosheets [5]. The combination of excellent photothermal and photodynamic abilities in BP-based nanodrug delivery systems can be used as the basis for the design of versatile multimodal therapeutic systems for cancer. Mei’s group has reviewed recent research and evaluated future possible BP preparations and biomedical applications in phototheray and theranostics for cancer [6]. Theranostic nanoagents combine imaging and therapeutic functions, enabling the simultaneous diagnosis and treatment of disease states. BP is an ideal biodegradable theranostic agent due to its inherent photoacoustic characteristics.

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and capability for the drug-loading of various fluorescent substances for both in vitro and in vivo imaging, in addition to PTT and PDT characteristics for therapy. It is anticipated that the rapid development of laser detection technology, when combined with nano-drug delivery systems, will lead to the development of novel ultra-fast integrated platforms for diagnosis and treatment, allowing additional early diagnosis of cancer and the rapid screening of large number of samples. Yu has previously reported that ultrasmall BP quantum dots modified by polyethylene glycol (PEG) could be used for photoacoustic (PA) imaging and photothermal ablation of tumors [7]. Liu and co-workers reviewed the latest progress in the development of 2D nanomaterials for cancer theranostic applications, suggesting that 2D BP nanosheets with high photothermal conversion efficiency and unique energy band structure properties can be used for PA-imaging-guided phototherapy [8]. Guo elaborated the applications of nano BP in biological imaging (fluorescence imaging, thermal imaging and photoacoustic imaging), disease treatment (optical therapy, light/chemical/immune synergistic therapy) and tumor nanocarriers [9]. However, as a novel class of 2D nanomaterials, BP nanosheets remain in the preliminary stages of theranostic application development, because additional systematic research is required.

Immunotherapy for cancer treatment has attracted increased attention over recent years. In the future, immune checkpoint inhibitors can be brought into BP-based nano-drug delivery systems to develop multi-modal synergistic anti-tumor nanoplatforms combining immunotherapy, gene therapy, chemotherapy, radiotherapy, photothermal therapy and photodynamic therapy to further enhance the selectivity and efficiency of the treatment of tumors while reducing their side effects. Recently, Mei coated erythrocyte membranes (RMs) over black phosphorus quantum dots (BPQDs) to form BPQD-RM nanovesicle (BPQD-RMNV)-mediated PTT biomimetic system, which could suppress residual and metastatic tumor growth in vivo when loaded with programmed cell death protein 1 (PD-1) antibody [10]. Subsequently, Mei designed a personalized photothermal vaccine combined with an antibody for PD-1 checkpoint blockade by coating surgically removed tumor cell membranes onto BPQD nanovesicles prior to loading them into a thermosensitive hydrogel, significantly enhancing tumor-specific CD8+ T cell elimination of surgical residual and lung metastatic tumors, effectively preventing their recurrence and metastasis [11]. Yang prepared self-assembled near infrared/reactive oxygen species (NIR/ROS)-sensitive BPQD vesicles grafted with PEG and active oxygen sensitive poly propylene sulfide, that were effective in blocking distant tumor growth and metastasis, and accomplishing effective photodynamic immunotherapy in vivo [12].

Besides the excellent biomedicine application, BP has also attracted extensive attention from the biosensing field. It is electrocatalytic for some reactions due to its band gap. The BP-based nanosystems possess of unique surface activity, photoelectric performance, and good biocompatibility, which is an ideal material for functionalizing the electrode or as specific signal reporters for implementing highly sensitive detection of biomarkers. The distinct fluorescence property of BPQDs and the fluorescence quenching of 2D BP nanosheets have been employed for preparing various fluorescence biosensors [9].

Compared with other nanomaterials such as graphene, exploration of BP remains at a preliminary stage. The study of BP in biomedicine faces significant challenges. The contradiction between stability and biodegradation is the primary aspect to be resolved. Due to the existence of a lone pair of electrons in its atomic structure, BP nanoparticles are easily oxidized and degrade into phosphoric acid in air or humid environments, severely limiting their application in physiological environments. On the other hand, that instability is conducive to biodegradation, which promotes the release of loaded anti-tumor drugs at the sites of tumors. The control of drug release from BP carriers only at the site of a tumor while maintaining their biostability in the blood circulation remains unclear. Appropriate methods that balance both the degradation and stability of BP should be explored.

Researchers have reported a variety of surface chemical modifications, including surface protective layers, surface chemical modifications and doping that enhance the stability of BP nanomaterials in physiological environments to a certain extent. Polydopamine (PDA) is a mussel-inspired material that can be used to adhere to the surface of a variety of materials through dopamine-oxidation self-polymerization under mild conditions [13]. The surface modification of BP materials with a PDA coating can produce a synergistic photothermal effect and increase the stability of BP [14]. Recently, Mei first reported the strategy of using the drug itself to stabilize BP. For example, the platinum-based anticancer drug DACHPt was utilized to coordinate with BP NSs to form the complex BP/DACHPt which improved stability. The simple strategy of drug-self-stabilized BP-based nanoplatforms opens a promising avenue for clinical applications of BP in cancer therapy [15]. Furthermore, it has been reported that mesenchymal stem cell transporting BP-based biocompatible PLGA nanospheres can enhance BP stability and provide photothermal therapy of glioma tumors [16]. In the future, a greater number of better methods will be explored that achieves controllable degradation of BP in vivo which can solve the contradiction between stability and drug release from BP nanomaterials.

The second challenge requiring verification is the toxicity and biosafety of BP nanomaterials. As is well known, the principal component of BP nanomaterials is phosphorus, an essential element in humans. Its degradation product, phosphoric acid, is also harmless, which has been confirmed by animal experiments. However, the degradation mechanisms and metabolic pathways of BP nanoparticles in humans have not been intensively studied, and so additional research remains to be conducted for use in the fields of medicine and biology. Xing et al. have performed a systematic cytotoxicity study of layered BP, in which BP of a large lateral size and thickness exhibited greater cytotoxicity. The smallest BP particles have shown only moderate toxicity [17]. In addition, whether long-term use of BP can cause excessive poisoning due to phosphate ions, such as loss of calcium and magnesium metal ions from the body, still requires long-term investigation. Furthermore, other effects on the
blood circulation and immune system also require additional study.

In conclusion, our perspective is that the recent efforts and investment in BP-based nano-drug delivery systems for tumor therapy have become the focus of global research and spawned multiple encouraging outcomes. Owing to the unique structure and characteristics of BP, it seems possible that the targeting strategy specifically for tumors can be expanded to alternative cancer-related events, such as those of the immune system or other biological organs or tissues, for which effective targeting is more realistically attainable. In order to enhance the therapeutic efficacy and promote the clinical applications of BP, it is critical for balancing the biodegradation and stability of BP-based nanocarriers. Thus, the appropriate modification of BP and maintaining its biostability in the blood circulation may be a good solution. Furthermore, the BP could also be utilized in a broader category of diseases, such as cardiovascular and cerebrovascular diseases, neurodegenerative disorders such as Alzheimer's disease, and mental disorders such as depression or anxiety.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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