Perspective

Chengyuan Hong, Zhusheng Liu, Tianxiang Chen* and Aiguo Wu*

Two-dimensional layered nanomaterials for tumor diagnosis and treatment

https://doi.org/10.1515/mr-2023-0006
Received February 4, 2023; accepted May 9, 2023;
published online June 14, 2023

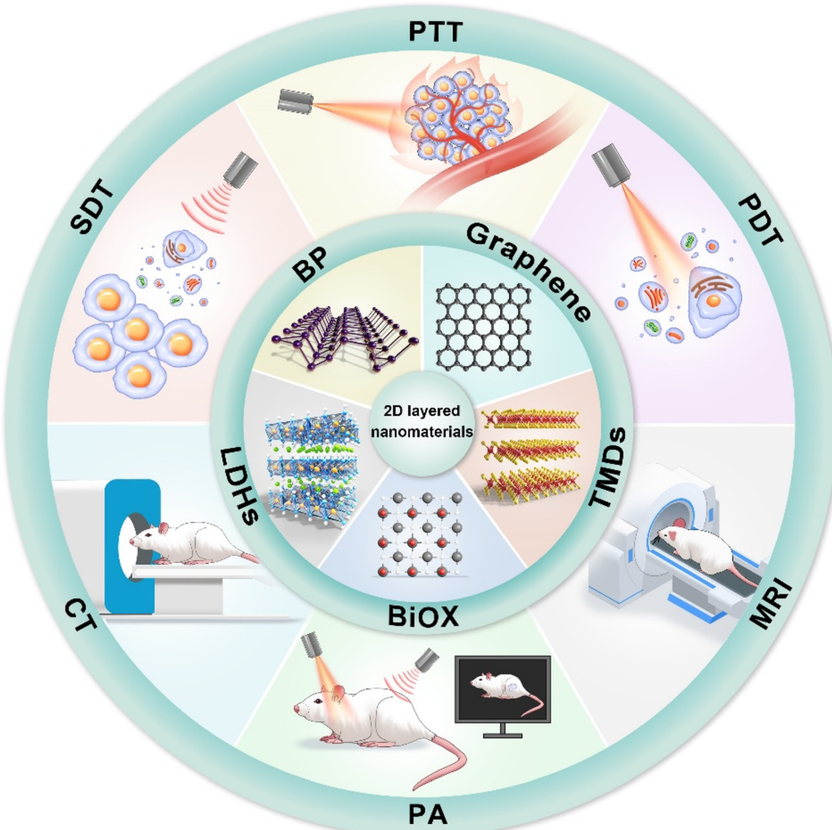
Abstract: With the evolution of nanomedicine, the past decades witnessed diversified nanomaterials as marvelous antitumor tools ushering in a new era of tumor diagnosis and treatment. Among them, two-dimensional layered nanomaterial as an emerging class of nanomaterials has one dimension less than 100 nm, showing a high specific area and the thinnest sheet-like structure (Liu S, Pan X, Liu H. Twodimensional nanomaterials for photothermal therapy. Angew Chem Int Ed 2020;59:5890–900). The discovery of graphene drove the exploration of various new two-dimensional layered nanomaterials for tumor diagnosis and treatment including graphene-based nanomaterials, black phosphorus (BP), transition metal dichalcogenides (TMDs), layered double hydroxides (LDHs), and bismuth oxyhalides (BiOX, X=F, Cl, Br, I) (Ma H, Xue MQ. Recent advances in the photothermal applications of two-dimensional nanomaterial: photothermal therapy and beyond. J Mater Chem 2021;9:17569). On the one hand, they exhibit strong near-infrared (NIR) absorption and the capacity of optimizing corresponding properties by adjusting the crystal structure. On the other hand, they own unique strengths such as fantastic physicochemical properties (graphene-based nanomaterials), high loading capacity (BP), distinct phase-dependent optical properties (TMDs), a specific chemical response to the tumor microenvironment (LDHs), and large X-ray attenuation coefficient (BiOX). Herein, we briefly introduce three typical two-dimensional layered nanomaterials, their prospects and future research priorities in tumor diagnosis and treatment are concluded.

Keywords: tumor diagnosis; tumor treatment; two-dimensional layered nanomaterials.

***Corresponding authors: Tianxiang Chen and Aiguo Wu**, Cixi Institute of Biomedical Engineering, International Cooperation Base of Biomedical Materials Technology and Application, CAS Key Laboratory of Magnetic Materials and Devices and Zhejiang Engineering Research Center for Biomedical Materials, Ningbo Institute of Materials Technology and Engineering, Chinese Academy of Sciences (CAS), Ningbo Key Laboratory of Biomedical Imaging Probe Materials and Technology, Ningbo 315201, Zhejiang Province, China, E-mail: chentx@nimte.ac.cn (T. Chen), aiguo@nimte.ac.cn (A. Wu). https://orcid.org/0000-0001-7200-8923 (A. Wu)
Chengyuan Hong, Cixi Institute of Biomedical Engineering, International Cooperation Base of Biomedical Materials Technology and Application, CAS Key Laboratory of Magnetic Materials and Devices and Zhejiang Engineering Research Center for Biomedical Materials, Ningbo Institute of Materials Technology and Engineering, Chinese Academy of Sciences (CAS), Ningbo Key Laboratory of Biomedical Imaging Probe Materials and Technology, Ningbo 315201, Zhejiang Province, China; and Department of Mechanical, Materials and Manufacturing Engineering, University of Nottingham Ningbo China, Ningbo, Zhejiang Province, China
Zhusheng Liu, Cixi Institute of Biomedical Engineering, International Cooperation Base of Biomedical Materials Technology and Application, CAS Key Laboratory of Magnetic Materials and Devices and Zhejiang Engineering Research Center for Biomedical Materials, Ningbo Institute of Materials Technology and Engineering, Chinese Academy of Sciences (CAS), Ningbo Key Laboratory of Biomedical Imaging Probe Materials and Technology, Ningbo 315201, Zhejiang Province, China

Introduction

With the evolution of nanomedicine, the past decades witnessed diversified nanomaterials as marvelous anti-tumor tools ushering in a new era of tumor diagnosis and treatment. Among them, two-dimensional layered nanomaterial as an emerging class of nanomaterials has one dimension less than 100 nm, showing a high specific area and the thinnest sheet-like structure [1]. The discovery of graphene drove the exploration of various new two-dimensional layered nanomaterials for tumor diagnosis and treatment including graphene-based nanomaterials, black phosphorus (BP), transition metal dichalcogenides (TMDs), layered double hydroxides (LDHs), and bismuth oxyhalides (BiOX, X=F, Cl, Br, I) (Scheme 1) [2]. On the one hand, they exhibit strong near-infrared (NIR) absorption and the capacity of optimizing corresponding properties by adjusting the crystal structure. On the other hand, they own unique strengths such as fantastic physicochemical properties (graphene-based nanomaterials), high loading capacity (BP), distinct phase-dependent optical properties (TMDs), a specific chemical response to the tumor microenvironment (LDHs), and large



Scheme 1: A scheme to illustrate the applications of two-dimensional nanomaterials in tumor diagnosis and treatment, including graphene-based nanomaterials, BP, TMDs, LDHs, and BiOX for computed tomography (CT), photoacoustic imaging (PA), magnetic resonance imaging (MRI), photodynamic therapy (PDT), photothermal therapy (PTT), and sonodynamic therapy (SDT).

X-ray attenuation coefficient (BiOX). Herein, we briefly introduce three typical two-dimensional layered nanomaterials, their prospects and future research priorities in tumor diagnosis and treatment are concluded.

Graphene-based nanomaterials

Based on the unique sp^2-hybridized crystal structure and the robust layered honeycomb lattice structure, graphene-based nanomaterials are not only endowed with intrinsic excellent photothermal conversion effect under NIR irradiation via the strong interaction between low-frequency photons and graphene, but also stand out as adaptive vehicles for loading varied therapeutic molecules and nanoparticles through conjunction reaction, hydrophobic interaction, and π-π stacking. In 2010, Liu et al. [3] first investigated the photothermal therapy (PTT) efficacy of PEG-grafted ultrasmall graphene oxide (GO) nanosheets *in vivo*. After two years, they proposed reduced graphene oxide (rGO) as improved PTAs, which displayed a 3-4-fold higher NIR absorption than GO derivatives [4]. The photothermal effect is the key mechanism for graphene-based nanomaterials to realize tumor treatment. On the one hand, photoinduced heat causes cell death or irreversible damage. On the other hand, the rising temperature increases blood flow to the tumor tissue and improves the permeability of the cell membrane, accelerating the anticancer drug's entry into tumor cells. On this ground, Chen and co-workers found the intracellular release of resveratrol had a five-fold increase after exposure to a 10 min NIR irradiation in the resveratrol-loaded rGO-PEG nanomaterial [5]. Besides, the combination with other functional molecules brings graphene-based nanomaterials extra therapeutic and diagnosis outcomes. For example, coupling with photosensitizer leads to enhanced photonic treatment performance. Santos et al. [6] demonstrated that methylene blue incorporated GO nanomaterial is capable for facilitating photothermal and photodynamic therapy (PDT) under 808 and 660 nm NIR irradiation, respectively. Moreover, by doping boron to the single-layer graphene quantum dot, Zhang and co-workers developed an improved T_1 contrast agent for magnetic resonance imaging (MRI) [7].

Black phosphorus nanosheets

Black phosphorus is a direct-gap semiconductor with a thickness-dependent band gap ranging from around 0.3 eV (bulk) to 2.0 eV (single layer). It has a similar layered structure to graphene except for its puckered lattice arrangement and bilayer configuration. The distinct structure of BP endows it with a high surface-to-volume ratio, which leads to a better drug-loading capacity than other two-dimensional layered nanomaterials. And the unique electric structure brings BP excellent optical and photoinduced properties. Since phosphorus is essential for human body that BP has a good biosecurity in normal cells. In 2016, Mei and co-workers first found that DOX-loaded BP nanosheets generated local hyperthermia under 808 nm NIR irradiation, which benefits the PTT and the release of DOX, resulting in an enhanced synergetic PTT/Chemotherapy of tumor [8]. Li et al. [9] first used BP nanosheets for photoacoustic (PA) imaging to investigate the distribution and metabolism of it, which paves the way for BP in tumor imaging diagnosis. Recently, the selective anti-tumor behavior of BP was revealed by Yu and co-workers [10]. It was found that BP rapidly generates a large number of phosphate ions in response to the harsh intracellular environment after entering tumor cells, which ultimately induces cell apoptosis. While in normal cells, BP exhibits a great compatibility under mild intracellular environment. Thus, the concept of bioactive phosphorus-based therapy (BPT) was proposed, revealing a bright direction of nanomaterials in the field of tumor treatment.

Bismuth oxyhalides

Bismuth oxyhalides has an open-layered crystal structure, in which $[Bi_2O_2]^{2+}$ slabs are sandwiched by double halogen anionic slabs. Since contiguous slabs have opposite charges, it generates an internal electric field, which promotes the separation of photoinduced electron-hole pairs and benefits PDT/PTT/sonodynamic therapy performance. The absorption spectrum of BiOX varies with different halogen anions from ultraviolet to visible light. Based on the rapid response to visible light, BiOX was extensively studied in the field of photocatalysis. Inspired by the photocatalytic performance of Bismuth oxychloride (BiOX), in 2016, our group first reported the utilization of BiOCl nanosheets/nanoplates as the photosensitizer for UV-triggered tumor PDT [11]. To further improve the optical properties of BiOX, defect engineering can generate oxygen vacancies, significantly reduce the band gap, and extend the light absorption spectrum to NIR region, it is widely employed in BiOX nanomedicine. Hence, our group proposed the defected black bismuth oxychloride nanosheets for tumor photothermal therapy under 808 nm NIR irradiation [12]. The defected BiOCl nanosheets showed a photothermal conversion coefficient of ~40 %. Besides, BiOX stands out from two-dimensional layered nanomaterials for its high X-ray attenuation capacity that can be applied in computed tomography (CT) contrast agents. Dai et al. demonstrated the capability of defected BiOCl nanosheets for achieving the CT and PA imaging-guided photothermal therapy of tumors [13].

Conclusion and prospects

Two-dimensional layered nanomaterials gained a swift development in the biomedical field; however, even tremendous publications were reported, not a single case was ever applied. There are still challenges needed to be overcome, and we would like to share our perspectives on this research field:

(i) Developing smaller-size two-dimensional material.

For two-dimensional nanomaterials applied in the biomedical field, the smaller size means less aggregation in the physiological environment, less likely to be captured by the liver, and more easily to be metabolized out of the body. The majority of the two-dimensional nanomaterials were synthesized via the solution-based method, the shear force generated in the solution during the synthetic reaction plays a decisive role in the size of the as-synthesized nanomaterials. By coupling computational fluid dynamics (CFD), the shear forces and other related parameters can be simulated, thus, the size of the two-dimensional nanomaterials can be further predicted. We think the utilization of CFD for the synthesis of two-dimensional nanomaterials might be able to precisely control their size.

(ii) Improving the anti-tumor selectivity of two-dimensional nanomaterials.

To date, numerous nanoagents were developed for tumor treatment, but the lack of selectivity of nanomaterials to tumor cells makes damage to normal cells inevitable. However, inspired by the bioactive phosphorus-based therapy, the mechanisms of the distinct bioactivity induced by the interaction between layered nanomaterial and tumor microenvironment (TME) could be studied and applied to improve the anti-tumor selectivity of two-dimensional nanomaterials without affecting normal cells. For two-dimensional layered nanomaterials, their high specific surface area, and unique physicochemical properties generate special biological effects with TME, leading to the reinforcement of tumor elimination and targeting ability. Moreover, according to the characteristics of the TME, such as low pH, low oxygen content, and high concentration of glutathione, we can take advantage of the loading capacity of two-dimensional nanomaterials to design materials with relevant cytotoxic responses, which effectively improve their anti-tumor selectivity.

Acknowledgments: We are grateful to the Shanghai Synchrotron Radiation Facility (SSRF) in China for their help with the XANES beam Line and National Synchrotron Radiation Laboratory in Hefei, China.
Research funding: This work was supported by the National Natural Science Foundation of China (32025021, 31971292, and 32111540257), National Key R&D Program of China (2018YFC0910601, 2019YFA0405603), the Science & Technology Bureau of Ningbo City (2020Z094), and the Key R&D Program of Zhejiang Province (2020C03110).
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Not applicable.
Ethical approval: The local Institutional Review Board deemed the study exempt from review.

References

1. Liu S, Pan X, Liu H. Two-dimensional nanomaterials for photothermal therapy. Angew Chem Int Ed 2020;59:5890–900.
2. Ma H, Xue MQ. Recent advances in the photothermal applications of two-dimensional nanomaterial: photothermal therapy and beyond. J Mater Chem 2021;9:17569.
3. Yang K, Zhang S, Zhang GX, Sun XM, Lee ST, Liu Z. Graphene in mice: ultrahigh in vivo tumor uptake and efficient photothermal therapy. Nano Lett 2010;10:3318–23.
4. Yang K, Wan JM, Zhang S, Tian B, Zhang YJ, Liu Z. The influence of surface chemistry and size of nanoscale graphene oxide on photothermal therapy of cancer using ultra-low laser power. Biomaterials 2012;33:2206–14.
5. Chen J, Liu H, Zhao C, Qin G, Xi G, Li T, et al. One-step reduction and PEGylation of graphene oxide for photothermally controlled drug delivery. Biomaterials 2014;35:4986–95.
6. Santos MS, Gouvea AL, Moura LD, Paterno LG, Souza PE, Bastos AP, et al. Nanographene oxide-methylene blue as phototherapies platform for breast tumor ablation and metastasis prevention in a syngeneic orthotopic murine model. J Nanobiotechnol 2018;16:9.
7. Wang H, Revia R, Mu QX, Lin GY, Yen C, Zhang MQ. Single-layer boron-doped graphene quantum dots for contrast-enhanced in vivo T_1-weighted MRI. Nanoscale Horiz 2020;5:573.
8. Tao W, Zhu XB, Yu XH, Zeng XW, Xiao QL, Zhang XD, et al. Black phosphorus nanosheets as a robust delivery platform for cancer theranostics. Adv Mater 2017;29:1603276.
9. Sun CX, Wen L, Zeng JF, Wang Y, Sun Q, Deng LJ, et al. One-pot solventless preparation of PEGylated black phosphorus nanoparticles for photoacoustic imaging and photothermal therapy of cancer. Biomaterials 2016;91:81–9.
10. Pan T, Fu W, Xin HB, Geng SY, Li ZB, Gui HD, et al. Calcium phosphate mineralized black phosphorous with enhanced functionality and anticancer bioactivity. Adv Funct Mater 2020;30:2003069.
11. Xu Y, Shi ZZ, Zhang LE, Brown EM, Wu AG. Layered bismuth oxyhalide nanomaterials for highly efficient tumor photodynamic therapy. Nanoscale 2016;8:12715.
12. Fang QL, Xu Y, Luo LJ, Liu C, Li Z, Lin J et al. Controllable synthesis of layered black bismuth oxidechloride nanosheets and their applications in internal tumor ablation. Regen Biomat 2022;9:rbac036.
13. Dai C, Hu RZ, Wang CM, Liu Z, Zhang SJ, Yu LD, et al. Defect engineering of 2D BiOCl nanosheets for photonic tumor ablation. Nanoscale Horiz 2020;5:857.