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Review

Two-dimensional non-carbonaceous materials-enabled efficient photothermal cancer therapy

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ABSTRACT

Based on the unique two-dimensional (2D) planar nanostructure with atomic-thin thickness, abundant composition variations and the corresponding exceptional physiochemical/biological performances, the emerging inorganic 2D nanomaterials with high biocompatibility have been becoming one of the most promising material nanosystems of great potentials for applications in biomedicine. This review focuses on the unique photothermal-conversion property of several new representative 2D nanomaterials beyond graphene for photothermal conversion-based tumor hyperthermia and theranostic biomedicine, including transition metal dichalcogenides (TMDCs, such as MoS_2, WS_2, TiS_2 and Bi_2Se_3), black phosphorous (P), metal Pd nanosheets and their composite nanosheets. Based on high photothermal-conversion efficiency of these 2D nanomaterials, this review first highlights the design, synthesis and surface functionalization of 2D nanomaterials for photothermal therapy (PTT) ablation of cancer cells/tissues. The representative strategies of functionalizing these 2D nanomaterials for imaging-guided PTT and PTT-based synergistic cancer therapy are then discussed. The preliminary progresses on biosafety evaluation of these 2D nanomaterials were also briefly summarized and discussed. Finally, we discussed the state-of-art unsolved critical issues and challenges, and outlooked further research directions of 2D nanomaterials for potential clinical translation for PTT tumor ablation. It is believed that the fast development and promising performance of these biocompatible 2D materials can provide a highly efficient nanoplatform for combating cancer by hyperthermia.

Contents

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Introduction

Hyperthermia as an efficient cancer-treatment modality has attracted broad research attentions of scientific community on account of its high efficiency for cancer-cell killing and specific role for enhancing the therapeutic outcome of other treatment modalities, such as chemotherapy and radiotherapy [1]. For thermal treatment of diseases, it is facile to realize site-specific heating effect where only the lesion tissues can be heated while the temperature of normal organs and tissues keeps at normal level. Various heating modalities have been developed to generate the hot regions in tumors, including focused ultrasound [2–4], radiofrequency [5], magnetic field [1,6], microwave [7], light [8,9], etc. Comparatively, photothermal therapy (PTT) features low cost, site-specific therapy, mitigated side effects and relatively high efficiency [10]. However, light-induced thermal treatment suffers from the difficulties/challenges of high light absorption of normal tissues and low light-penetration depth, which reduce the heating efficiency and cause the non-specific damage to normal tissue along light-propagation path. Fortunately, recent developments of nano-biotechnology provide a highly efficient and versatile strategy to overcome above-mentioned critical issue to large extents. Nanoparticles (NPs) with high photothermal-conversion efficiency are introduced into tumor tissues, which can be activated by light at reduced laser intensity/power density and specific laser wavelength in the first (700–980 nm) and second (1000–1400 nm) biological window [11–15]. As a result, such NPs-assisted PTT strategies can simultaneously increase the tumor-ablation efficacy and mitigate the side effect during the hyperthermia process.

Metal NPs such as Au nanorods, nanocages, nanostars and nanoshells have been extensively developed as the earliest candidates for photothermal cancer ablation, but their optical properties are substantially influenced by their particle size, morphology, photothermal stability and even surrounding microenvironment [13,16–18]. Carbon-based nanosystems including mesoporous carbon [19–21], carbon nanodots[22,23] and graphene [24,25] were also explored in biomedical applications, especially in photothermal therapy based on their strong light absorption in NIR region and corresponding high photothermal-conversion efficiency [26]. Some organic, inorganic and their hybrid nanosystems, such as polypyrrole [27], indocyanine green[28], conductive polymers [29], CuS [30,31], Prussian blue [32], WO_x [33], black TiO_2 [34] and other organic polymer/molecules[35,36] also provide alternative photothermal agents for PTT.

Most of reported photothermal agents are in spherical or rod-like morphology [13,16,17,37–42]. The loading capability and efficiency of these solid nanosystems are severely limited though some cage-like shape can be created within the matrix. Fortunately, recent results have demonstrated that inorganic two-dimensional (2D) nanosheets with ultrathin atomic thickness, controllable lateral size, and extremely large surface area exhibit unique physiochemical properties suitable for a broad range of applications, especially in biomedicine such as drug/gene delivery [43–45], diagnostic imaging [46,47], photothermal/photodynamic therapy [38], biosensing[48] and even tissue engineering [49]. Compared to traditional photothermal agents, these 2D nanosheets feature low toxicity, easy surface modification and high photothermal-conversion efficiency at the wavelength within the biological window. Graphene-based 2D nanosheets have been extensively explored as the efficient photothermal agents for tumor hyperthermia [50]. However, graphene oxide or reduced graphene suffer from potential toxicity and extremely low biodegradation, similar to the toxicity of carbon nanotubes [51–53]. In addition, their photothermal efficiency should be further improved to enhance the ablation outcome, which is relatively difficult to realize because of their single carbonaceous composition. The fast development of 2D materials recently catalyzes the emergence of a new non-carbonaceous 2D material family with high biocompatibility and enhanced photothermal-conversion efficiency, mainly including transition metal dichalcogenides (TMDCs), black phosphorous, metals and their corresponding composites (Fig. 1a). These 2D materials can be easily synthesized either by liquid exfoliation from their bulk crystals (up-down method) or growth from corresponding precursors in solution (bottom-up approach, Fig. 1a) [54–66]. The up-down approach can produce 2D nanosheets with very few defects in the materials, but it is difficult to control the morphology and uniformity of nanosheets by the exfoliation process. Comparatively, the bottom-up approach can fabricate 2D nanosheets with desirable morphology, size, dispersity and even surface modification, but it is still challenging to synthesize 2D nanosheets with single atomic-layer thickness and few defects by the bottom-up strategy, which are more suitable for biomedical applications. Importantly, either abundant chemical composition variations or subsequent functionalization processes can endow these 2D photothermal agents with bio-imaging property, i.e., these multifunctional 2D nanomateirals possess theranostic functions (concurrent diagnostic imaging and therapy) [67]. In addition, these new 2D nanosystems can realize high synergistic therapy (Fig. 1a), such as combined PTT/chemotherapy and PTT/radiation therapy (RT). As a matter of fact, a large number of 2D material nanosystems have been developed with rich composition variations and multi-facet physiochemical properties, which can circulate within the blood vessels and accumulate into tumor tissue. Upon external laser irradiation, these 2D nanosheets can convert the photo energy into thermal energy, increase the local tumor temperature and cause the tumor ablation (Fig. 1b). When they are designed and chosen for biomedical hyperthermia applications, a careful consideration should be kept in mind that there should be a good balance between biosafety and photothermal performance of these 2D materials while the biosafety is the priority (Fig. 1b). The chosen 2D materials must be highly biocompatible so that they can be potentially developed for further clinical translation. If they are toxic, it will be impossible for clinical translation no matter how high their PTT efficiency could reach.

Based on the fast development of new 2D materials for biomedicine, herein we highlight and discuss the very recent progresses on the design, synthesis, functionalization and photothermal applications of new emerging non-carbonaceous 2D nanomaterials, focusing on their unique structure/composition-property relationships in tumor hyperthermia. The biosafety issues regarding short- and long-term biocompatibility evaluation of these 2D materials is briefly discussed, with a careful consideration of their structure/composition control to satisfy the practical-application requirements. Especially, the research obstacles/challenges and future developments of these promising 2D nanomaterials for clinical translation are discussed and outlooked.

Transition metal dichalcogenides

Transition metal dichalcogenides (TMDCs) are a new family of 2D nanosheets typically in the form of MX_2 where M is the transition metal and X is the chalcogen [54,62,68]. The diverse composition choice of TMDCs enables this new material family with distinguished electronic, optical and catalytic properties, which underpin a broad spectrum of applications in energy, environmental and biomedical areas [57,69–74]. Recent results have demonstrated that certain members of TMDCs were featured with low cytotoxicity, high hemo/histocompatibility and high photothermal-conversion efficiency [75–81]. Especially, their high biocompatibility and biosafety guarantee their potential applications in biological- and biomedicine-related fields [82–93]. In