Science Bulletin 64 (2019) 1707–1727

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Science Bulletin
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Review

Two-dimensional nanomaterials: fascinating materials in biomedical field

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ARTICLE INFO

Article history:
Received 23 July 2019
Received in revised form 22 August 2019
Accepted 12 September 2019
Available online 20 September 2019

Keywords:
2D nanomaterials
Drug delivery
Tissue engineering
Biosensing

ABSTRACT

Due to their high anisotropy and chemical functions, two-dimensional (2D) nanomaterials have attracted increasing interest and attention from various scientific fields, including functional electronics, catalysis, supercapacitors, batteries and energy materials. In the biomedical field, 2D nanomaterials have made significant contributions to the field of nanomedicine, especially in drug/gene delivery systems, multimodal imaging, biosensing, antimicrobial agents and tissue engineering. 2D nanomaterials such as graphene/graphene oxide (GO)/reduced graphene oxide (rGO), silicate clays, layered double hydroxides (LDHs), transition metal dichalcogenides (TMDs), transition metal oxides (TMOs), black phosphorus (BP), graphitic carbon nitride (g-C_3N_4), hexagonal boron nitride (h-BN), antimonene (AM), boron nanosheets (B NSs) and tin telluride nanosheets (SnTe NSs) possess excellent physical, chemical, optical and biological properties due to their uniform shapes, high surface-to-volume ratios and surface charge. In this review, we first introduce the properties, structures and synthetic strategies of different configurations of 2D nanomaterials. Recent advances and paradigms of 2D nanomaterials in a variety of biomedical applications, ranging from drug delivery, cancer treatment, bioimaging and tissue engineering to biosensing are discussed afterwards. In the final part, we foresee the development prospects and challenges of 2D nanomaterials after summarizing the research status of ultrathin 2D nanomaterials.

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1. Introduction

Ultrathin two-dimensional (2D) nanomaterials are a new class of nanomaterials with sheet-like structures and transverse dimensions larger than 100 nm, while the thickness is typically less than 5 nm [1]. Due to their unique shapes, 2D nanomaterials possess large surface and anisotropic physical/chemical properties [2]. The study of 2D nanomaterials was first reported in 2004, when Novoselov et al. [3] succeeded in exfoliating graphene from graphite. Graphene is a one-atom-thick and crystalline carbon film, with various unexpected properties such as excellent transparency, electrical/thermal conductivities, large specific surface area, and extraordinary mechanical properties [4]. The success of graphene has reignited interest in other ultrathin 2D nanomaterials. So far, relevant investigation has led to a large number of 2D nanomaterials being discovered [5,6]. For example, silicate clays [7,8], layered double hydroxides (LDHs) [9,10], transition metal dichalcogenides (TMDs) [11,12], transition metal oxides (TMOs) [13], black phosphorus (BP) [14–17], graphitic carbon nitride (g-C_3N_4) [18,19], hexagonal boron nitride (h-BN) [20,21] antimonene (AM) [22–24], boron nanosheets (B NSs) [25] and tin telluride nanosheets (SnTe NSs) [26] are all typical 2D nanomaterials with similar structural features and possess various properties (Fig. 1). Notably, these 2D nanomaterials have broad application prospects in catalysis [27], optoelectronic [28], energy storage [29], biomedicine [30], sensors [31], supercapacitors [32], batteries [33] and so on.

Due to their mechanical/chemical/optical properties, biocompatibility and degradability, 2D nanomaterials are widely used in drug/gene delivery [34,35], biosensing [36–38], multimodal imaging [39,40], antimicrobial agents [41,42], tissue engineering [43,44], and cancer therapy [37,45]. As the thinnest materials, 2D nanomaterials have the highest specific surface areas among all known materials, which means they have large reservoirs and anchoring sites to efficiently load and deliver therapeutic agents [46]. Meanwhile, the planar nanostructure endows these nanomaterials with special physio-chemical properties (e.g., light, ultrasonic and magnetic responses) and biological behaviors such as endocytosis, biodistribution, biodegradation and excretory

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https://doi.org/10.1016/j.scib.2019.09.021
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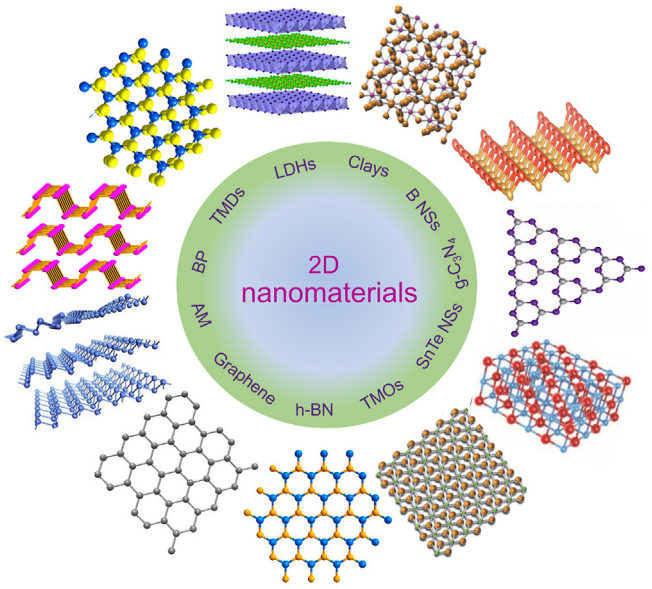

Fig. 1. (Color online) Schematic illustration of 2D nanomaterials including carbon-based nanomaterials, silicate clays, LDHs, TMDs, TMOs, BP, g-C_3N_4, h-BN, AM, B NSs and SnTe NSs.

pathways, which lead to their employment in various biomedical applications [47–49].

As far as we know, the superior biomedical performance of 2D nanomaterials has been discussed in previous reviews [2,23,46], but few of them have been focused on the comprehensive profiles of 2D nanomaterials, especially in drug delivery, tissue engineering and biosensing, which possesses great significance to the biomedical development of 2D nanomaterials. In this review, state-of-the-art biomedical applications of 2D nanomaterials from drug delivery to biosensing are discussed. Firstly, we briefly introduce the properties, structures and synthetic strategies of different configurations of 2D nanomaterials for a comprehensive understanding of nanomedicine. Then, we summarize and discuss recent advances and paradigms of 2D nanomaterials in versatile biomedical applications, including drug delivery, combined therapy, bioimaging, tissue engineering and biosensing in detail. Finally, we foresee the development prospects and challenges of 2D nanomaterials after summarizing the research status of ultrathin 2D nanomaterials.

2. Composition and structures of 2D nanomaterials

Although the composition and crystal structures of all 2D nanomaterials are significantly different, they still can be categorized as layered 2D nanomaterials and non-layered 2D nanomaterials. In layered nanomaterials, atoms on the plane are connected by strong chemical bonds in each layer, while layers stack together to form bulk crystals through a weak van der Waals interaction [50]. A typical representative of layered materials is graphite [51]. Other layered materials include silicate clays, LDHs, TMDs, TMOs, BP, g-C_3N_4, h-BN, AM, B NSs and SnTe NSs are the main subjects of this review. By contrast, non-layered nanomaterials crystallize in three dimensions through atomic or chemical bonds to form bulk crystals, such as polymers and metal oxides/chalcogenides [52].

For layered nanomaterials, many reliable methods for preparing ultrathin 2D nanosheets have been developed, which can be classified into top-down and bottom-up approaches [53]. The top-down method relies on driving forces to break the weak van der Waals interaction between layers, and exfoliate layered 2D crystals into single or few-layer nanosheets, such as mechanical cleavage, sonication-assisted liquid exfoliation, ion-intercalation and exfoliation [53–55]. The bottom-up method is based on direct synthesis of ultrathin 2D nanosheets from different precursors by chemical reactions under certain conditions, including wet-chemical synthesis (templated synthesis, hydro/solvothermal synthesis, self-assembly of nanocrystals and soft colloidal synthesis) and chemical vapor deposition (CVD) [55,56].

The crystal structures of layered 2D nanomaterials are described briefly. The atomic arrangements of 2D nanomaterials greatly determine their biological and physicochemical properties. A few atoms thickness in the vertical dimension makes them extraordinary as compared with other materials [57]. Graphene is an allotrope of carbon composed of a compact hexagonal network, in which carbon atoms are interconnected by covalent sp^2 bonds [1]. By contrast, with the same hexagonal carbon atoms as graphene, GO contains not only sp^2 bonds but also sp^3 bonds, offering rich surface chemical properties owning to the existence of oxygenated groups [60]. Meanwhile, this further increases the type of interactions that can occur on GO surface. In addition, rGO, an intermediate state between graphene and GO, can be easily synthesized by the chemical or thermal reduction of GO via various methods [58]. Since, rGO still retains some oxygen functional groups after reduction, its concentration of structural defects is higher than that of graphene [59].

Different from those 2D nanomaterials with a single atom thickness, several 2D materials like silicate clays, LDHs, TMDs and TMOs consist of stable single crystal units. For instance, as a synthetic clay mineral, laponite consists of layered units in which two tetrahedral silica sheets are sandwiched within an interior octahedral layer containing Mg^{2+} cations. Individual laponite crystals are typically disk-shaped with a diameter and thickness of 25 and 0.92 nm respectively, and an empirical formula expressed as $Na^{+}_{0.7}[(Si_8Mg_{5.5}Li_{0.3})O_{20}(OH)_4]^{-0.7}$ [60], in which lithium cations randomly substitute magnesium (Mg) cations in the structure. As a result, the cations substitution process endows these laponite crystals with net negative face charges and positive edge charges. LDHs, whose general formula is expressed as $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2](A^{n-})_{x/n}\cdot mH_2O$ (M^{2+} and M^{3+} are bivalent and trivalent cations respectively, and A^{n-} acts as the charge-balancing and exchangeable interlayer anion), are various kinds of host-guest layered materials containing positively charged metal host layer and negatively charged interlayer anion as well as water molecules [61]. Because of the comparatively feeble interlayer bonding, organic and inorganic anions can be inserted into the interlayer of LDHs to compensate the positive charge of host layer.

Like silicate clays and LDHs, TMDs are MX_2-type layered compounds where M stands for a transition metal element (such as Mo or W) and X represents a chalcogen (such as S, Se, or Te) [62]. TMDs have a three layered atomic structure with a transition metal layer sandwiched between two chalcogen layers. Each TMDs monolayer is roughly 0.7 nm thick with a triangular lattice structure. Due to their planar characteristic, TMDs exhibit a large surface-to-volume ratio [63], which is conducive to functionalization. 2D TMOs are composed of oxygen atoms and transition metals, and their different structures depend on their individual components. Many remarkable properties of TMOs are governed by the cationic species and their changeable oxidation state. In addition, a variety of bandgaps exist in TMOs, providing the possibility of designing optical and electric characteristics at almost any desired wavelength [13].

Like graphene, BP is only made up of the phosphorus element, and its puckered honeycomb structure is formed by the bonding of one P atom with another three P atoms, exhibiting strong P—P bonds [64]. Other ultrathin 2D nanomaterials with similar structures to graphene include g-C_3N_4 and h-BN. G-C_3N_4 is a graphene

analogue and possesses a van der Waals layered structure, which is formed through the sp^2 hybridization of carbon and nitrogen atoms [65]. h-BN exhibits a hexagonal structure consisting of an equal number of boron and nitrogen atoms [21]. A monolayer h-BN nanosheet is commonly known as the "white graphene".

AM, a new semiconductor, possesses a layered structure similar to BP, but the distance between atoms out-of-plane is shorter than that of BP, indicating stronger interlayer interactions [66]. Element boron (B), as the closest to carbon (C) in the periodic table, has received extensive attention. Pure B has been made into B NSs with nanoscale thickness, in which the B atoms are covalently bonded [67,68]. As a cubic crystal structured semiconductor (0.18 eV at 300 K), SnTe NSs are compose with element Sn and Te, which are two essential elements for human [69,70].

3. Graphene-based 2D nanomaterials for biomedical applications

The graphene family usually includes three members: graphene, GO, and rGO. Graphene is hailed as the "new wonder nanomaterial". The unique layered structure of graphene makes it the thinnest nanomaterial with monoatomic thickness. Compared with carbon nanotube, graphene has a higher specific surface area, which is conducive to functionalization [34]. As to GO, it is obtained by the partial oxidation of graphene. In other words, different types of oxidative functional groups (e.g., hydroxyl, carboxyl, or epoxy) can be introduced into graphene structure to form GO, increasing its hydrophilicity and making it easier for functionalization [71]. RGO, a substitute for pure graphene, can be easily produced by removing most of the oxygenated groups from GO. In contrast with GO, rGO has more sp^2 carbon, exhibiting a higher absorbance in the near-infrared region (NIR) [72]. Studies have utilized graphene and its derivatives in numerous biological applications such as gene/drug delivery, biosensors, bioimaging, antifungal activity and bioengineering, owning to their unprecedented electrical/thermal conductivities, versatile chemistry, mechanical strength and biocompatibility [73]. Since a large number of researches have reported the biomedical application of graphene-based materials, in this section, we will focus on some representative examples published lately in drug/gene delivery, tissue engineering and biosensing.

3.1. Graphene

As a relatively new treatment, gene therapy can treat various diseases caused by genetic disorders. Functionalized graphene has been widely exploited in gene delivery. For example, a biocompatible and efficient gene delivery vector for graphene modified with polyamidoamine (PAMAM) dendrimer and oleic acid was reported [74]. Cell culture experiments showed that the graphene-oleate-PAMAM hybrids exhibited excellent gene transfection capacity, which was 13 times higher than that of ultrasonicated graphene. In addition, graphene-based nanomaterials have been developed to induce cell necrosis. A recent report showed that few-layer graphene (FLG) has specific killing effect on monocytes without toxic or active effect on other immune function cells [75]. This therapeutic activity of FLG has been used in myeloid monocytic leukemia. Moreover, the higher specificity and toxicity of FLG were confirmed when compared with chemotherapy drug etoposide.

Graphene is being explored in tissue engineering owning to its unique properties. Tissue engineering is an important new medical strategy that combines cells, biochemical factors and engineered materials to restore, maintain or improve the function of tissue or organ [76]. In a recent study, a graphene hydrogel (MGH) membrane consisting of multiple, chemically converted graphene (CCG) sheets by face-to-face stacking (Fig. 2) was fabricated by Lu et al. [77] to investigate its performance in guided bone regeneration (GBR). The results showed that CCG-based membranes could effectively maintain bone space, promote early osteogenesis, accelerate mineralization, and improve bone quality and bone regeneration rate. The MGH membranes remained *in situ* 8 weeks after implantation, indicating that the surface texture of MGH membranes was conducive to their adhesion to bone tissues. This study effectively demonstrated CCG' s potential in GBR treatment and biological tissue engineering.

In another study, a surface plasmon resonance (SPR) biosensor based on graphene was developed for the detection of biomolecules. Zeng et al. [78] advanced the field by designing a novel biosensor based on graphene-gold metasurface to realize directly unlabeled ssDNA detection through the pi-stacking interaction between graphene and ssDNA. The graphene sensing substrate was prepared from the pristine graphene layers, and showed good optical and electronic properties as well as high electron transfer rate and optical transparency, leading to a strong plasmon enhancement effect. As reported, the detection limit of graphene-gold biosensing structure on ssDNA was 1×10^{-18} mol/L, higher than that of SPR biosensor. Based on the foregoing discussion, it is not difficult to conclude that graphene plays an important role in multisensor platform design for effective diagnosis of human diseases.

3.2. GO

Due to the existence of primitive graphite structure and oxygen-containing functional groups, as well as the coexistence of hydrophobic and hydrophilic properties, GO exhibits not only good water dispersion and biocompatibility, but also a high affinity for some drug molecules. Motivated by these properties, GO nanosheets are widely used as drug carriers to enhance therapeutic effect. In addition, due to the strong NIR absorption, GO is often used as the photothermal therapy (PTT) agent. For example, Yin et al. [79] developed a hyaluronic acid-decorated GO nanosheet (HSG) with a strong loading of doxorubicin hydrochloride (DOX, chemotherapeutics drug) (Fig. 3). Results of *in vivo* and *in vitro* tests indicated that such a nanosystem could achieve the photothermal controlled selective rapid drug delivery, as well as photo-chemo synergetic therapy.

As one of the most typical 2D nanomaterials, GO has been selected to develop tissue engineering. For instance, Ruan et al. [80] constructed GO-based biocompatible scaffolds by covalent cross-linking GO with carboxymethyl chitosan (CMC). The resulting porous GO-CMC scaffolds showed significantly higher modulus and hardness compared with CMC scaffolds. Moreover, the π-π stacking interactions of GO sheets led to the enhancement of osteoinductivity of GO-CMC scaffolds. Systematic *in vitro* and *in vivo* experiments demonstrated that these GO-CMC scaffolds exhibited remarkable effect in repairing the skull defect of rats, providing new insights into regenerative medicine and tissue engineering. Additionally, the unique and versatile properties of GO bring many opportunities to the development of advanced biosensors. An advantageous immunosensing platform based on GO coated nanopaper (GONAP) was prepared by Cheeveewattanagul et al. [81]. The photoluminescence-quenching character of GONAP enabled it to quench the photoluminescence of quantum dots integrated with antibodies (Ab-QDs). When these antibodies were bound to antigens, they could form antigen-Ab-QD complex and then be desorbed from GONAP, restoring the photoluminescence. Such a highly sensitive platform represents a virtually universal immunosensor method, exhibiting ready-to-use immune sensing properties. The assay was proved to be effective in the analysis of

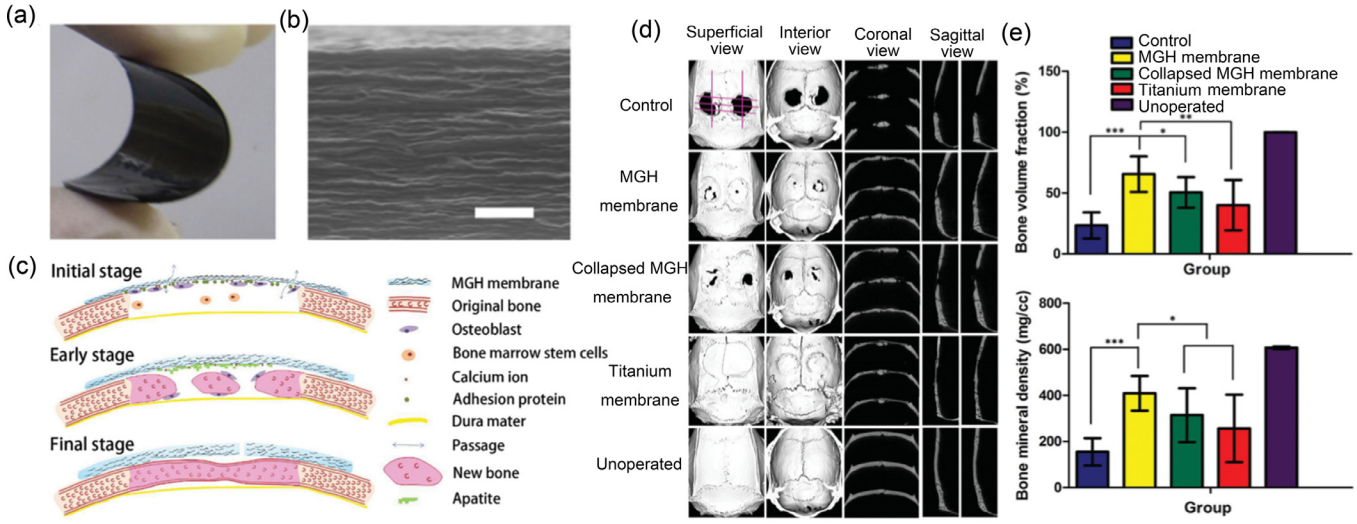

Fig. 2. (Color online) MGH membranes for tissue engineering. (a) Photograph of the MGH membrane, and (b) the corresponding transmission electron microscope (TEM) image of the cross section of MGH membrane. (c) Healing process of a calvarial defect using MGH membranes as a barrier membrane. (d) Micromorphological analysis of calvarial defects after treatment including ultrasound, and internal, coronal and sagittal views of microcomputed tomography images taken at 8 weeks postoperatively. (e) Bone volume fraction and bone mineral density analyzed after 8 weeks of surgery. Reproduced with permission from Ref. [77], Copyright © 2016, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

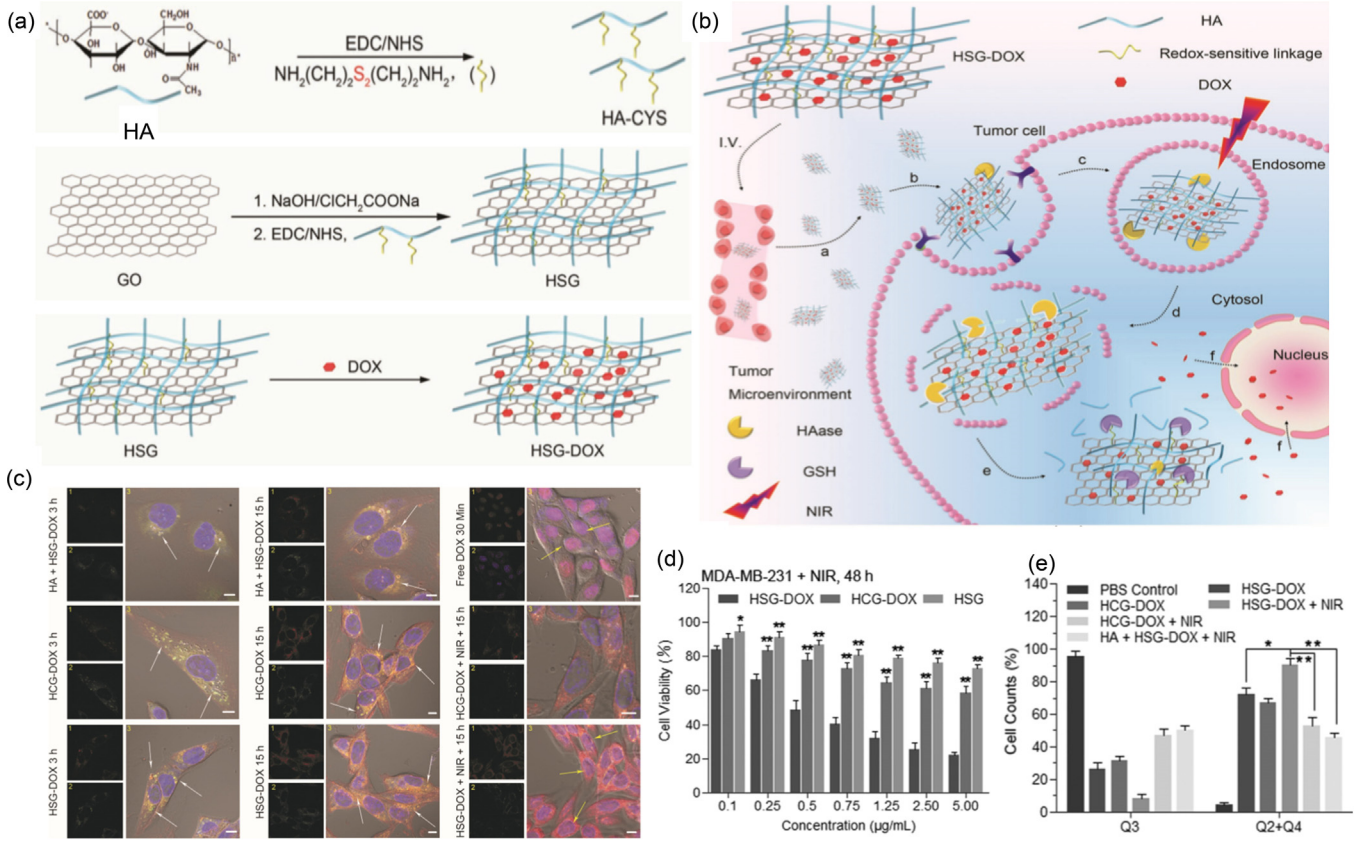

Fig. 3. (Color online) HSG for drug delivery. (a) Synthesis process of HSG-DOX nanosheets. (b) NIR irradiation-controlled tumor cytoplasm-selective delivery and glutathione (GSH)-triggered rapid release of DOX. (c) Confocal laser scanning microscopy (CLSM) images of MDA-MB-231 cells under different conditions. (d) HSG, HSG-DOX, DOX with NIR laser irradiation after 48 h. (e) Flow cytometric analysis of MDA-MB-231 cell apoptosis induced by different formulations with or without NIR laser irradiation. Reproduced with permission from Ref. [79], Copyright © 2017, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

human serum. In a word, GONAP opens a way for immunosensing, which can be applied to automated diagnosis.

3.3. RGO

RGO is commonly obtained by reducing GO to remove most of its oxygenated functional groups, thus owning some structure defects of carbon nanosheets. The recovered graphitic network of rGO accounts for its high electrical conductivity [76]. With less oxygen content, surface charge, and hydrophilic functional groups than GO, rGO can also be assembled via non-covalent interactions (van der Waals forces and π-π stacking) to effectively adsorb drug or biomolecules. Various studies have demonstrated that rGO has good biocompatibility and excellent electrical conductivity, therefore is widely used in drug delivery, PTT, tissue engineering and biosensing [73].

With a large specific surface area and good electrochemical properties, rGO has become a research hotspot in drug delivery system. He et al. [82] designed an electrochemically triggered drug delivery system on the basis of DOX-loaded rGO thin films, in which the DOX was combined with rGO via π-π stacking and hydrophobic interaction. The loading efficiency of DOX onto rGO was influenced by pH, and the maximal loading rate was 98% at pH 9. In another study, a rGO-based PTT agent was developed for effective cancer treatment. Yan et al. [83] designed multifunctional rGO-based nanosheets containing indoleamine-2,3-dioxygenase inhibitors (IDOi), which triggered PTT to destroy primary tumors under NIR laser irradiation. At the same time, the IDOi released by rGO nanosheets at the tumor sites could modulate the catabolism of tryptophan, thus enhancing the antitumor immune response. Both *in vitro* and *in vivo* experiments revealed that IDOi/rGO nanosheets could synergistically induce systemic antitumor immunity and directly kill tumor cells under laser irradiation.

In addition, rGO has also been successfully tested in tissue engineering. Huo et al. [84] designed rGO-enzyme-coated tissue-engineered blood vessels (TEBVs) to inhibit platelet aggregation, in which rGO functioned as a carrier to support two enzymatic catalysts, apyrase and 5-nucleotidase (5-NT) for cascading reactions (Fig. 4). These rGO-enzyme complexes could catalyze the conversion of adenosine diphosphate (ADP) to adenosine monophosphate (AMP) and further transfer AMP to adenosine, thereby inhibiting ADP-induced platelet aggregation and thrombosis. Undoubtedly, this work provides a new strategy for the construction of TEBV.

RGO-based materials have also been extensively studied as biosensors because of their availability and electrical conductivity. As a paradigm, a new type of nanocomposite material composed of rGO/Rh nanoparticles was prepared to construct a sensitive electrochemical enzyme biosensor for the detection of 17β-estradiol [85]. 17β-estradiol is listed as an emerging contaminant because it is harmful to the endocrine functions of animals and humans. This rGO-based biosensor could successfully detect 17β-estradiol with an ultralow detection limit of 0.54 pmol/L and a high sensitivity of 25.7 A $(\mu mol/L)^{-1}$ cm^{-1}, thus achieving the diagnosis of endocrine function. Based on these results, such biosensors based on rGO nanomaterials can be applied to the rapid and accurate determination of hormones in urine samples.

3.4. Summary of graphene-based 2D nanomaterials for biomedical applications

In summary, graphene-based nanomaterials (graphene, GO, and rGO) are very appealing due to their flat honeycomb nanostructures and unparalleled performance. Recent advances in the synthesis and functionalization of graphene-based materials have brought new possibilities to their biomedical applications including drug delivery, cancer treatment, tissue engineering and biosensing. However, long-term adverse effects must be considered when designing graphene-based nanomaterials for biomedical applications. As a result, it is of great importance to study the toxic mechanism for the purpose of designing and manufacturing graphene-based nanocomposites safely. Future research may focus

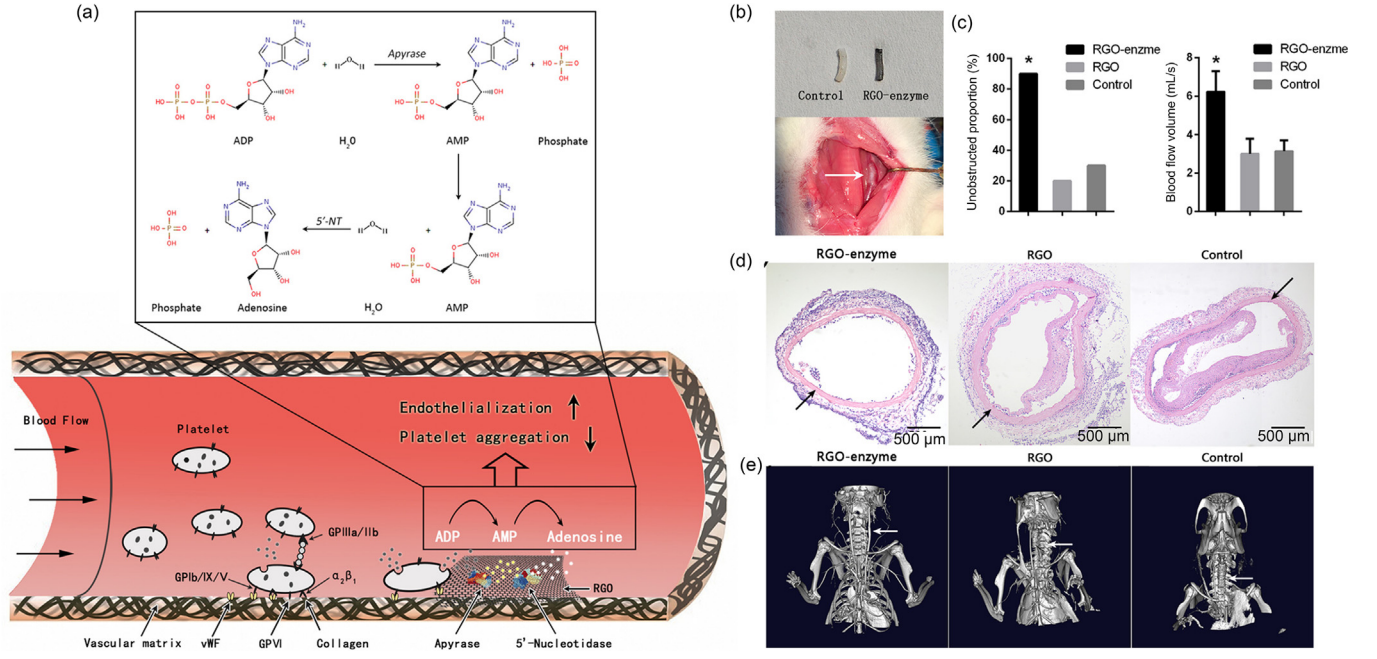

Fig. 4. (Color online) RGO-based TEBVs for antiplatelet function. (a) Construction process of RGO-enzyme-coated TEBV for inhibition of platelet aggregation. (b) RGO-enzyme-coated TEBV and controlled TEBV, and the arrow indicated implanted TEBV on day 7. (c) The unobstructed proportion of TEBV on day 7. (d) HE staining of TEBVs on day 7. (e) Microcomputed tomography angiography on day 7 under different conditions. Reproduced with permission from Ref. [84], Copyright © 2017, American Chemical Society.

on exploring more fundamental biological reactions of graphene-based nanomaterials, such as systematic assessment of the physical and chemical properties associated with toxicity, to optimize biological applications with minimal safety risks.

4. Silicate clays for biomedical applications

In recent years, the interest in silicate clays has increased dramatically because they can be easily modified for different purposes. Smectite is one of the most common types of clays with a crystal structure. It has an octahedral alumina sheet sandwiched between two tetrahedral silica sheets in multiple layers [86]. Clays are characterized by aqueous stability, high drug loading, shear thinning, etc. The distinct layered structure of clays enables their surfaces to carry permanent negative charge and the edges to carry positive charge [87]. Because of these advantages, the use of clays has been expanded to the pharmaceutical industry, where clays are used for drug delivery, tissue engineering and biosensing [88–90]. In this part, recent advances in the biomedical application of clays are reviewed in detail.

Over the past decade, silicate clays have inspired tremendous research interest in gene or drug delivery for their incomparable biological safety [34,91]. In addition to biocompatibility, they also have other excellent properties that benefit delivery systems. For example, the adsorption of silicate clays on nucleic acid and drug molecules exhibits structural stability, which can prevent biological molecules from degradation or destruction in rigorous conditions. Moreover, compared with other vectors, silicate clays are safe and high efficient therapy carriers to validly avoid severe immunological and toxicological responses [92,93]. Recently, Jesus et al. [94] constructed a clay-based nanocomposite by incorporating sodium montmorillonite (MMT) into a hybrid hydrogel of siloxane-poly(ethylene oxide) to deliver sodium diclofenac (SDCF). This hybrid hydrogel nanocomposite could realize the sustained release of SDCF, offering the possibility of long-term treatment of arthritis, sprains, gout, migraine, and postoperative pain.

In other studies, silicate nanomaterials were developed for tissue engineering applications [95]. Scientists designed a nanocomposite hydrogel using laponite nanosilicates and gelatin methacrylate (GelMA) to control the rapid release of growth factor-rich stem cell secretome [96]. The nanocomposite hydrogel loaded with secretome provided a dual therapeutic system through its ability to promote angiogenesis and protect the heart, possessing the potential to improve the therapeutic efficacy of stem cell-derived secretome for cardiac tissue repair and regeneration. Another strategy for tissue engineering is incorporated a small amount of laponites (XLG) with the silated hydroxypropylmethyl cellulose (Si-HPMC) hydrogel [97]. The prepared composite hydrogel led to the development of a hybrid interpenetrating network, improving the mechanical properties of the hydrogel. The physicochemical properties and *in vitro* cytocompatibility of the composite hydrogel were also evaluated. The results showed that the composite hydrogel could improve the cell survival rate and increase the number of cell clusters. Based on these preliminary results, Boyer et al. [97] finally concluded that Si-HPMC/XLG hydrogel combined with chondrocytes had potential application value in cartilage tissue engineering.

Another example of tissue engineering is the application of silicate clays to hemostasis because these 2D natural clays can activate blood platelets to induce blood coagulation. For example, Gaharwar et al. [98] successfully synthesized nanocomposite hydrogels composed of silicate nanoplatelets and gelatin, which could be used as injectable hemostatic agents to promote *in vitro* and *in vivo* blood coagulation (Fig. 5). The results demonstrated that the addition of silicate nanoplatelets to gelatin could significantly improve the physiological stability, injectability and hemostatic performance, and reduce the *in vitro* blood clotting time by 77%. *In vivo* tests further indicated that these nanocomposites had good biocompatibility and could promote hemostasis in lethal liver laceration. With such unique properties, these newly developed silicate-based gelatin nanocomposites could be used as injection hemostatic agents to treat emergent wounds outside the hospital.

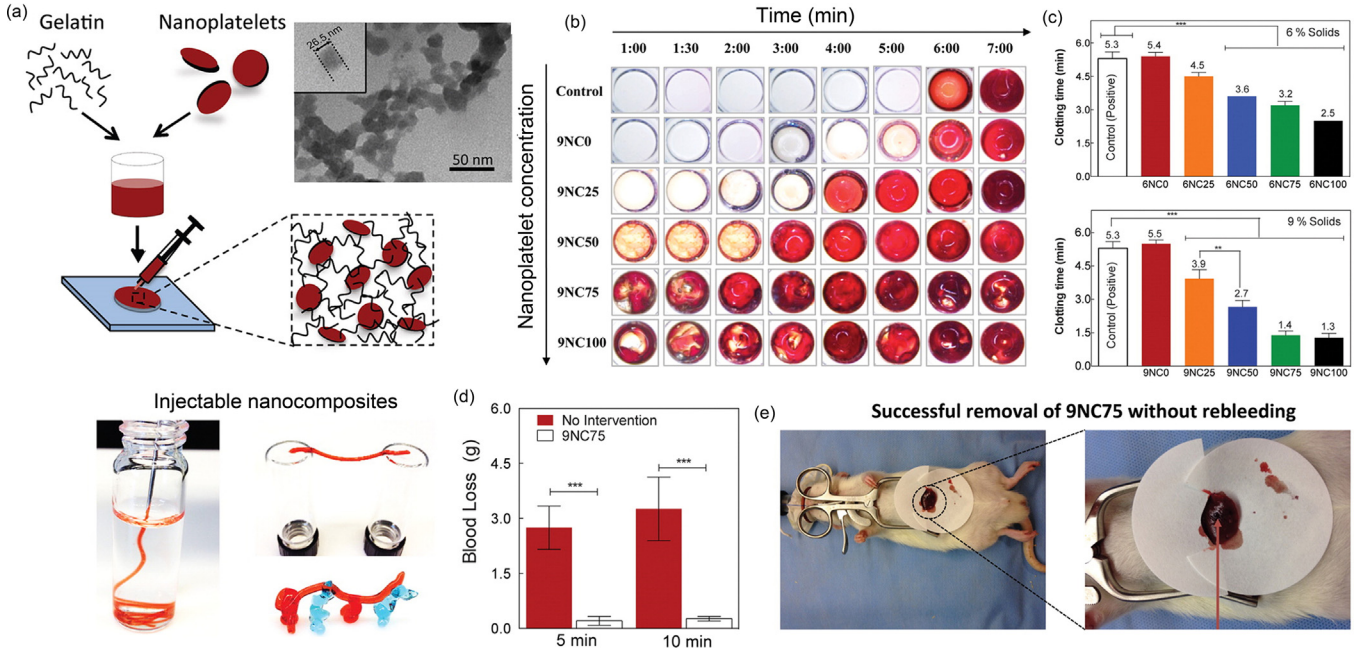

Fig. 5. (Color online) Silicate nanoplatelets-based nanocomposite hydrogels as hemostatic agents. (a) Synthetic schematic of nanocomposite gels. (b), (c) Effect of nanocomposite hydrogels on the clotting whole blood. (d) Effect of nanocomposite hydrogels on preventing blood loss. (e) The small amount of nanocomposite hydrogels was enough to stop bleeding. Reproduced with permission from Ref. [98], Copyright © 2014, American Chemical Society.

In summary, various biological applications of silicate clays have been presented in this part, which greatly improves the comprehension of clays as a potential biomaterial for medical applications. The shape and surface charge properties of silicate clays allow them to interact with biomolecules. It is expected that abundant transformation research based on silicate clays will be conducted in fields of biosensing, immunomodulation and cancer treatment.

5. LDHs for biomedical applications

As a class of 2D nanomaterials, LDHs have been widely explored as inorganic-biology composite materials for biomedical applications, owning to their good stability, excellent biocompatibility and the versatility in chemical composition [99–101]. Typically, LDHs are composed of a layer of metal atoms sandwiched between hydroxide layers, possessing a high layer charge density, which can realize chemical modifications or interlayer composition changes [102]. Due to their unique 2D structure, LDHs are versatile in both host layers and interlayer anions, and have the ability to non-covalently bind anionic drug molecules and imaging material with low toxicity, thus attracting research interest in drug delivery, bioimaging, tissue engineering and biosensing.

Studies have demonstrated that LDHs can exhibit pH-sensitive drug release. For instance, a recent work reported by Peng et al. [100] used LDHs to develop a biocompatible nano-delivery system (Fig. 6). Gd^{3+}-doped monolayer LDH nanosheets (MLDH) were successfully synthesized with a novel bottom-up synthesis method. As drug carriers, MLDH nanosheets could achieve the co-loading of DOX and indocyanine green (ICG, photothermal and photodynamic agent), showing an unprecedentedly high loading of DOX&ICG (797.36%) and 99.67% of encapsulation efficiency. Since ICG could realize an efficient photothermal conversion for its strong NIR optical absorption, the prepared DOX&ICG/MLDH composite showed

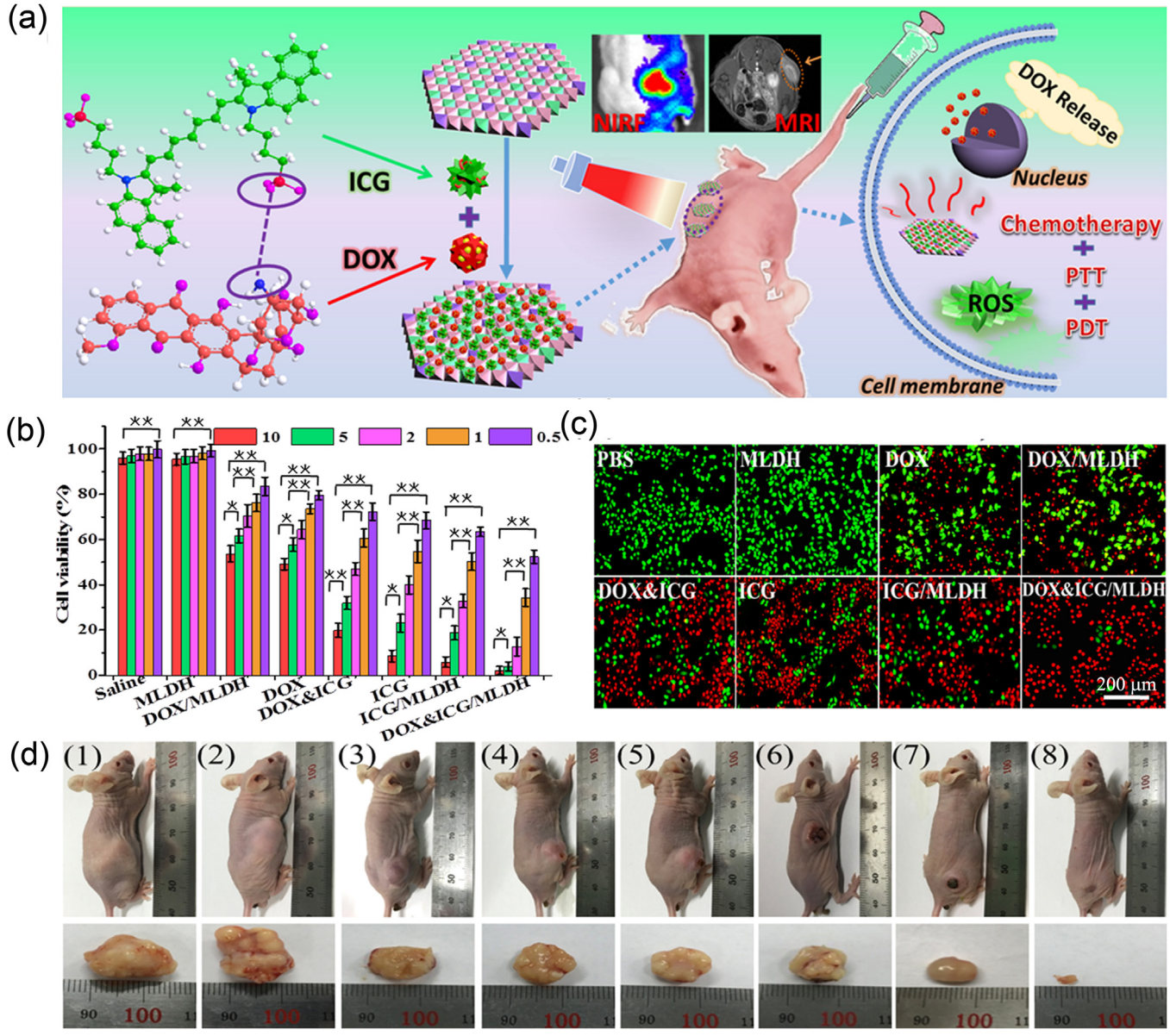

Fig. 6. (Color online) Application of LDHs in drug delivery. (a) A schematic diagram of drug delivery system based on MLDH for efficient loading of theranostic agents. (b) Relative viability of HepG2 cells after incubation with various drugs at different concentrations upon NIR irradiation and (c) the corresponding Calcein-AM/PI staining images. (d) Digital photographs of the mice on day 14 after various treatments. Reproduced with permission from Ref. [100], Copyright © 2018, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

both pH and NIR induced DOX release. Meanwhile, this drug formulation could produce a large number of reactive oxygen species (ROS), demonstrating the synergistic treatment of chemotherapy, PTT, and photodynamic therapy (PDT). *In vitro* and *in vivo* therapeutic evaluations demonstrated that DOX&ICG/MLDH nanocomposite material revealed a superior synergetic anticancer activity and excellent biocompatibility.

In addition, due to the tunable composition of host layers, specific imaging functions can be achieved via changing the metal elements of layers. In a recent report by Mei et al. [101], rare-earth (Gd^{3+} and Yb^{3+}) co-doped LDH single-layer nanosheets (Gd&Yb-MLDH) were prepared by one-step "bottom-up" method, showing a uniform morphology. With the successful introduction of Gd^{3+} and Yb^{3+} into the host layer of LDH, the Gd&Yb-MLDH single-layer nanosheets exhibited superior magnetic resonance (MR)/computed tomography (CT) dual-mode imaging performance. By further combining with ICG, SN38&ICG/Gd&Yb-LDH showed tri-mode imaging including near infrared fluorescence (NIRF) imaging, MR imaging (MRI) and CT imaging, demonstrating a noninvasive visualization of drug bio-distribution with high sensitivity and spatial resolution. *In vivo* tests verified that SN38&ICG/Gd&Yb-LDH achieved a complete tumor ablation, showing excellent synergetic chemo/PTT/PDT theranostics performance.

LDHs are also widely applied to tissue engineering in recent years. It is well known that LDHs possess compositional flexibility. Therefore, the biocompatibility and osteogenic differentiation of LDHs can be improved by substituting the bivalent cations and trivalent cations with necessary bioactive elements like Mg, iron (Fe) and strontium (Sr). Taking the advantage of the above characteristics, Cao et al. [103] fabricated an Ag-loaded MgSrFe-LDH/Chitosan (Ag-MgSrFe/CS) composite scaffold for bone tissue engineering. In this work, CS, a typical natural material, provided a favorable microenvironment for cell proliferation. Mg played a crucial role in bone metabolism and regeneration, while Sr and Ag showed antibacterial activity and anabolic activity. The prepared composite scaffold exhibited excellent cellular compatibility, osteogenic activity and antibacterial properties, showing extensive clinical application prospects in tissue engineering.

Although LDHs are insulators, they can also be used as biosensors, in which electrical conductance can be provided by other materials. Wang et al. [104] successfully designed a non-enzymatic glucose sensor based on CuAl-LDHs modified glassy carbon electrode. Due to the excellent electrocatalytic activity of copper-based materials used for the oxidation of glucose, the prepared CuAl-LDHs sensor exhibited high sensitivity, fast response (less than 5 s) and low detection limit (0.02 μmol/L) in the determination of glucose. Moreover, the sensor also exhibited strong anti-interference ability in the presence of ascorbic acid, acetaminophen, uric acid and other carbohydrate compounds. Therefore, it could be used for the rapid and efficient determination of glucose in human blood samples.

In conclusion, as a new kind of 2D nanomaterials, LDHs possess excellent anion exchange capacity, good biocompatibility and drug delivery potential, therefore can be used in drug delivery, tissue engineering, biosensing and other biomedical fields without obvious side effects. However, there are still some drawbacks of LDHs in preparation method and functionalization, therefore more breakthroughs of LDHs-based biomedical applications are expected.

6. TMDs for biomedical applications

As one of the most widely used 2D materials, TMDs, which are composed of a layer of transition metal atoms sandwiched with two layers of chalcogen atoms to form a hexagonal lattice, have attracted extensive attention in fields of catalysis, energy materials, electronics and more recently biomedicine [105]. Due to their ultrathin atomic monolayer or multilayer structure, TMDs possess distinctive physicochemical and biological properties, arousing a great deal of interest from researchers. In addition, as semiconductors, TMDs possess an electronic bandgap which increases as the thickness decreases [106]. These properties establish the important role of TMDs in drug/gene delivery, cancer treatment and biosensors.

Drug delivery systems are conducive to drug targeted transport and alleviate side effects. With excellent biocompatibility and low cytotoxicity after functionalization, TMDs can also be used as the drug or gene delivery systems in the biomedicine field. For example, Liu et al. [107] functionalized MoS_2 nanosheets with lipoic acid modified polyethylene glycol (LA-PEG) via thiol reaction to enhance the physiological stability and biocompatibility. The extraordinary surface-area-to-mass ratio of MoS_2 nanosheets achieved highly efficient loading of DOX. As a result, MoS_2-PEG loaded with DOX could realize the combination of PTT and chemotherapy without noticeable toxicity. This was the first time when TMDs was used as a new 2D nanocarrier for drug delivery and tumor synergetic therapy. In another work, researchers designed a MoS_2-based nanocomposite modified with polyethylenimine (PEI) and PEG via disulfide bonds [108]. Due to the positive charge of MoS_2 nanosheets and negative charge of nucleic acid molecules, the MoS_2-PEI-PEG nanocomposite could interact with DNA through electrostatic interaction, showing promising potential for gene delivery.

With the continuous development of biomedicine, various TMDs have been employed for simultaneous imaging diagnosis and cancer therapy. TMDs can also respond to such tumor microenvironment (TME) as pH, glutathione (GSH), H_2O_2, etc. therefore can be used to pH-sensitive starving therapy, GSH sensitive imaging, and chemodynamic therapy (CDT) [109,110]. However, since most TMDs cannot be rapidly excreted from the body, they bear the risk of chronic toxicity due to accidental ingestion of non-specific organs as well as long-term removal of nanoparticles. To address this problem, Guan et al. [111] developed polyvinyl pyrrolidone (PVP) coated Fe_3S_4 tetragonal nanosheets (TNSs) by a hot-injection thermal decomposition reaction. The PVP coated Fe_3S_4 TNSs had strong near-infrared absorption, resulting in excellent photothermal conversion efficiency (64.3%), infrared thermal (IRT) imaging and great T_2-weighted MRI. In addition, Fe_3S_4 TNSs could achieve the synergism of PTT/CDT, because the localized heat generated by PTT could enhance the Fenton process by utilizing the excessive H_2O_2 in the TME, while the hydroxyl radicals (·OH) produced by this process could inhibit tumor growth. Therefore, such an inorganic theranostic platform could be applied to MR/IRT imaging guided PTT/CDT. More importantly, TNSs could effectively accumulate in the tumor while gradually transform to ultrasmall FeOOH particles, completing the clearance from the body after one month. All in all, the PVP coated Fe_3S_4 TNSs-based body-clearable theranostic platform has provided a new approach to the design of inorganic pharmaceutical preparations for clinical applications in the future.

Another biomedical application of TMDs stems from their unique optical, electrical and mechanical properties, making them promising candidates for biosensor. Chen et al. [112] fabricated CVD-grown monolayer MoS_2-based bioabsorbable, multifunctional transient sensors to monitor critical parameters related to the recovery of traumatic brain injury, such as intracranial pressure, temperature, motion and strain (Fig. 7). Experiments in living animal models successfully confirmed the ability of these sensors to measure intracranial parameters in mice. Such a technology plays a clinically relevant role in diagnostic/therapeutic functions,

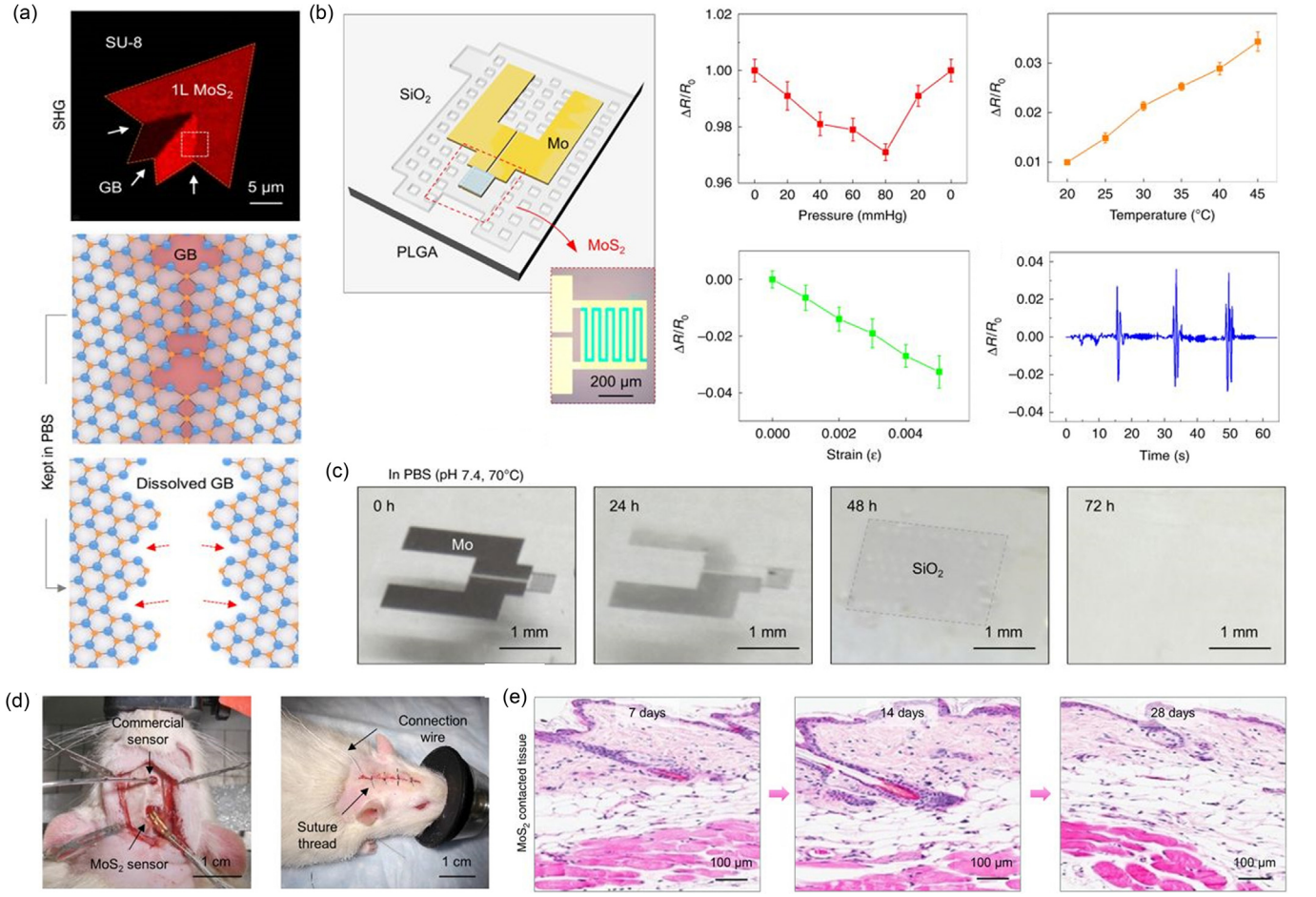

Fig. 7. (Color online) Application of TMDs to biosensors. (a) Morphological and structural evolution of CVD-grown monolayer MoS_2 crystals with different dissolution times in PBS solution. (b) Schematic of the structure of a MoS_2-based sensor and its characteristic responses as a function of pressure, temperature, strain, and acceleration. (c) Optical images of the sensor in PBS solution with different dissolution times. (d) Optical images of a MoS_2-based bioabsorbable sensor implanted in a rat. (e) Histological images of tissues surrounding the implanted MoS_2 for 4 weeks. Reproduced with permission from Ref. [112], Copyright © 2018, Nature Publishing Group.

paving the way for the integration of more 2D materials into sensing platforms as well as temporary biomedical implants.

To sum up, in this section, recent development of TMDs in biomedical fields including drug/gene delivery, biosensor, PTT and CDT have been summarized and discussed. In spite of the remarkable progress, there are still tremendous challenges in the clinical application of TMDs. The synthesis and modification methods need to be optimized for preparing multifunctional TMDs with lateral size, specific thickness and crystal phase. Additionally, more emphasis should be placed on evaluating toxicology profiles of TMDs nanomaterials before their possible clinical translation.

7. TMOs for biomedical applications

Besides the aforementioned well-known TMDs, TMOs are also notable 2D nanomaterials. The transition metal s-orbital electrons of TMOs are held strongly by the oxygen atoms, hence the structural and physicochemical properties of TMOs are mainly determined by d-orbital electrons [13]. Due to their wide bandgaps, TMOs nanosheets show remarkable photochemical and electric properties [113]. Moreover, some of the TMOs can directly interact with biomolecules after surface modification. These appealing properties enable the multiple biomedical applications of TMOs in targeted drug delivery, cancer therapy, tissue engineering, biosensing, etc. Currently, most of the published researches focus on two well-studied materials: manganese dioxide (MnO_2) and titanium dioxide (TiO_2).

MnO_2 nanosheets consist of an edge-sharing metal oxide octahedral unit with ultra-sensitivity to the mild acidity to break up and release Mn^{2+} ions, leading to their wide application in drug delivery and biosensor [114–116]. As a paradigm, a recent work by Chen et al. [114] constructed an intelligent theranostic platform based on DOX-loaded 2D MnO_2 nanosheets to achieve ultrasensitive pH-triggered T_1-weighted MRI and drug delivery. All these experimental results showed that MnO_2-based theranostics agents with dual pH-responsive functions could realize successful cancer treatment. In another similar study, Fan et al. [117] developed intelligent 2D theranostic nanomaterials by anchoring upconversion nanoprobes (UCSMs) onto MnO_2 nanosheets for simultaneous pH-/H_2O_2 responsive upconversion luminescent (UCL) imaging and oxygen-elevated synergetic radiotherapy (RT)/PDT (Fig. 8). MnO_2 nanosheets underwent decomposition in acidic TME to recover the quenched upconversion luminescence of UCSMs. Moreover, through reaction with H_2O_2 to produce massive oxygen, MnO_2 significantly improved the synergistic PDT/RT effect under NIR/X-ray irradiation.

Different from other 2D TMOs, MnO_2 nanosheets possess facile redox activity which can oxidize multiple reductants such as GSH and ascorbic acid [118,119]. With this oxidation ability, MnO_2 nanosheets were developed as biosensors to detect reduction reagents. Yan et al. [120] designed a sensitive and convenient

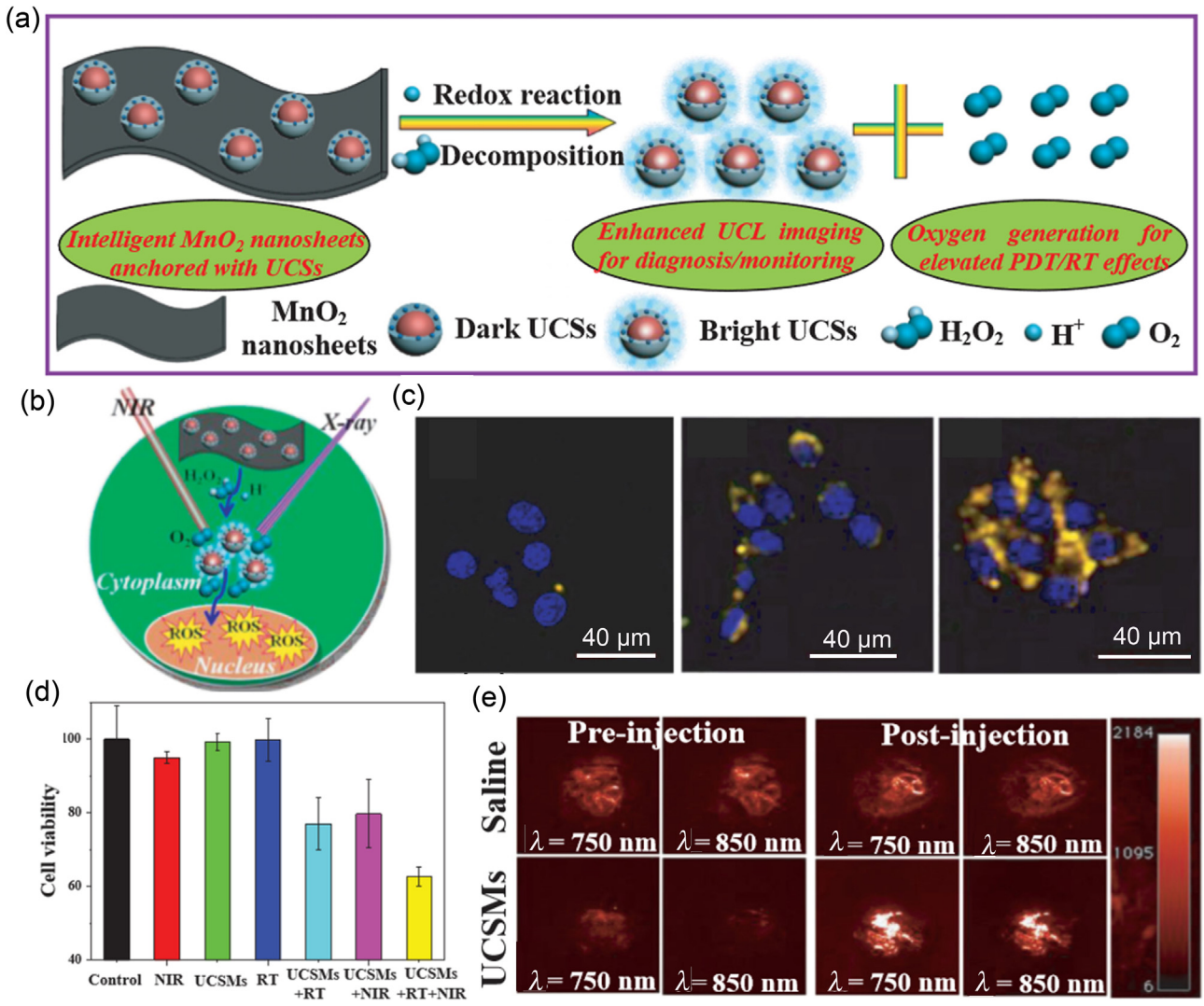

Fig. 8. (Color online) TMOs for UCL imaging and synergetic therapy. (a) Schematic illustration of MnO_2 nanosheets decomposed in acidic H_2O_2. (b) Schematic illustration of the UCL imaging and oxygen-elevated PDT/RT by using MnO_2-based UCSMs. (c) CLSM images of hc-4 T_1 cells after incubation with UCSMs. (d) Viability of hc-4 T_1 cells in the presence of UCSMs upon NIR/X-ray irradiation. (e) Photoacoustic (PA) images of 4 T_1 solid tumors under different conditions. Reproduced with permission from Ref. [117], Copyright © 2015, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

fluorescent "turn off-on" sensing platform on the basis of ultrathin MnO_2 nanosheets and graphene quantum dots (GQDs) for the rapid and selective detection of GSH in living cells. In this platform, MnO_2 nanosheets could quench the fluorescence intensity of GQDs by fluorescence resonance energy transfer. What's more, MnO_2 nanosheets could be selectively reduced to Mn^{2+} cations by GSH, which was beneficial to the release of GQDs as well as the sufficient recovery of fluorescent signal. Therefore, the dual functions of MnO_2 nanosheets as fluorescence quencher and GSH discriminator in this sensing platform made it available to measure the intracellular GSH concentration. The proposed nanosensor exhibited excellent merits in GSH-associated disease monitoring.

As to TiO_2, it has significantly different properties but a similar structure to MnO_2. As a semiconductor, TiO_2 possesses good optical absorption at UV region to generate $^1O_2$, making it possible to act as PDT agent [121]. Much effort has been devoted to developing TiO_2-based nanocomposite for inhibiting electron-hole pair recombination and expanding the light response to visible region. For example, Shang et al. [122] successfully prepared rGO-TiO_2 composite via a simple hydrothermal reduction method recently. Compared with unmodified TiO_2, the absorption spectrum of rGO-TiO_2 composite extended from UV to visible light region, which effectively improved the photodynamic treatment performance. Thus, the rGO-TiO_2 composite provide a new strategy for PDT. In another application, nanocomposite hydrogels were prepared by combining TiO_2 nanosheets with acrylamide, mimicking some physicochemical properties of articular cartilage [123]. The key of this technique is to use a strong magnetic field to align TiO_2 nanosheets in a coaxial manner. As a research paradigm, this nanocomposite is very prospective in biological tissue engineering.

It is clear from the above discussion that the application of TMOs in drug delivery, PDT and biosensing derives from their unique properties (redox activity and various photoelectric properties). MnO_2 nanosheets are widely used for their redox properties, while TiO_2 nanosheets for their photocatalytic and dielectric properties. As many other 2D nanomaterials, although the biocompatibility of TMOs has not been fully evaluated, further study based on these existing photoelectric properties in the biomedical field is still very encouraging.

8. BP for biomedical applications

As a representative non-metallic layered semiconductor, BP is formed by its puckered layers through weak van der Waals forces,

and can be exfoliated into ultra-thin 2D nanosheets [124]. Compared with other 2D nanosystems (e.g., graphene, TMDs), the development of BP nanosheets' biomedical application is much slower due to the lack of mature synthetic strategies as well as their instability in air and water. However, with the rapid development of nano-synthetic technology and 2D materials chemistry, the biomedical application of ultrathin BP nanosheets has made significant breakthroughs.

Ultrathin BP nanosheets exfoliated from bulk BP can be used as photosensitizer to generate $^1O_2$ within the entire visible light region, which was reported by Wang et al. [125] for the first time. The water dispersible BP nanosheets showed notable cancer treatment ability in both *in vitro* and *in vivo* studies. In subsequent studies, it is found that BP nanosheets can be used as carriers for the delivery of therapeutic agents due to their high surface area. Recently, Chen et al. [126] reported a novel DOX loaded multimodal therapeutic system on the basis of BP nanosheets (Fig. 9). The drug release could accelerate in the acidic TME and further promoted under NIR irradiation owning to the excellent photothermal effect of BP nanosheets. Such a drug delivery system exhibited pH-/photo-responsive release characteristics and realized synergistic PTT/PDT/chemotherapy. In another similar study, Tao et al. [127] also designed a DOX loaded delivery platform based on BP NSs. The innovation of this work was to reveal the endocytosis pathways and biological activities of PEGylated BP NSs, that is, BP NSs was transported through "micropinocytosis" → "late endosomes" → "lysosomes", and autophagy was involved in the degradation of PEGylated BP NSs.

In addition to serving as therapeutic agents for drug/gene delivery, PTT and PDT, BP nanosheets possess intrinsic abilities of cellular bioimaging and tumor PA imaging. For example, Lee et al. [128] employed a modified ultrasonication-assisted solution method to prepare BP nanodots from BP nanosheets, which exhibited intriguing optical properties in biological imaging. After an efficient endocytosis of BP nanodots, HeLa cells showed obviously blue or green fluorescence upon exposure to laser irradiation at 358 or 400 nm, indicating a potential application for cellular tracking or fluorescence imaging. In another example, Sun et al. [129] reported TiL_4 (a sulfonic ester of the titanium ligand) coordinated BP quantum dots (BPQDs) as efficient PA agents in bioimaging. The resulting TiL_4@BPQDs showed enhanced stability in water dispersions after surface coordination. Moreover, this material displayed better PA performance at 680 nm than that of AuNRs owing to its larger NIR extinction coefficient. *In vitro* and *in vivo* experiments further

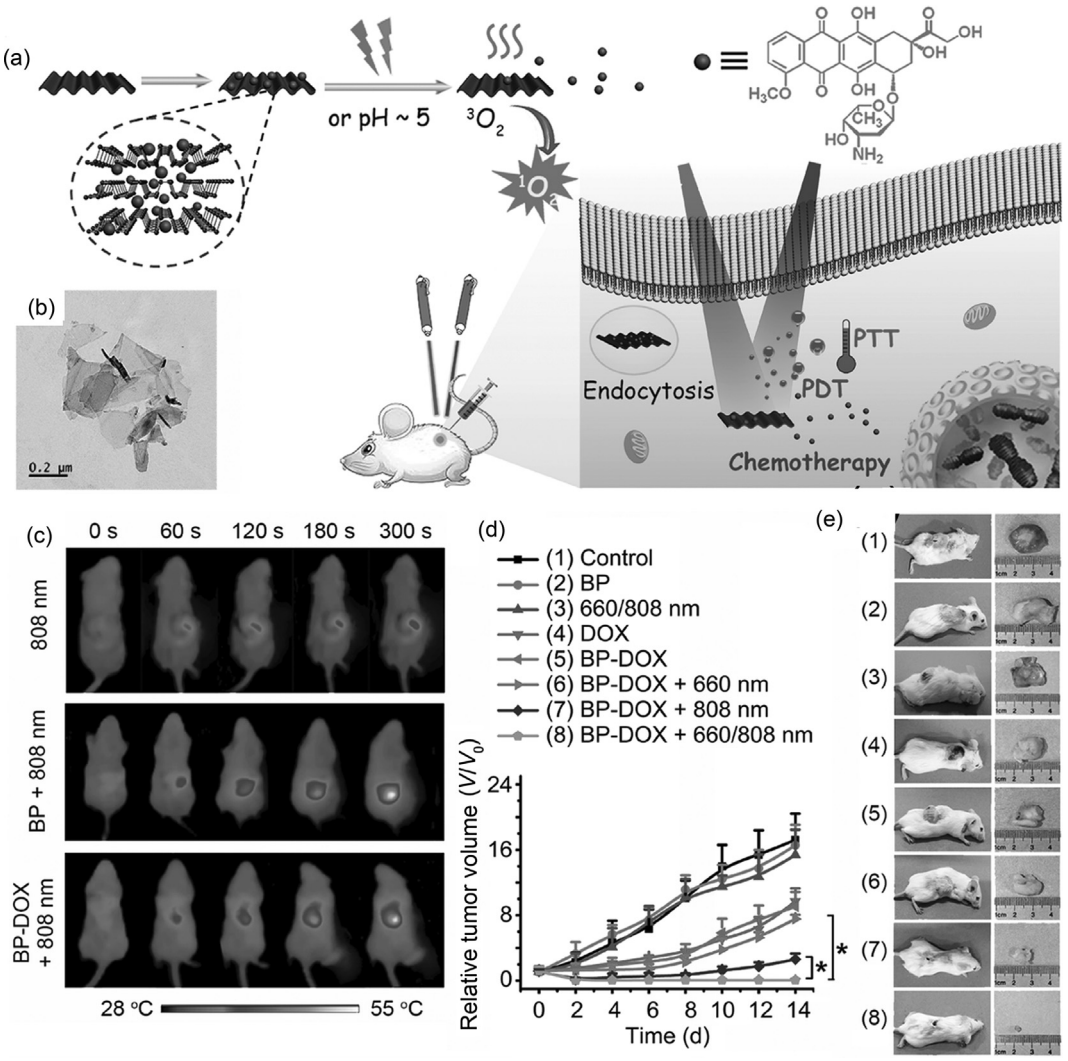

Fig. 9. BP nanosheets for drug delivery and synergistic therapy against cancer. (a) The scheme of BP-based drug delivery system for concurrent and synergistic PDT/PTT/chemotherapy of cancer, and (b) the corresponding TEM image of BP nanosheets. (c) NIR thermal images of tumor-bearing mice after the injection of BP and BP-DOX with 808 nm laser irradiation. (d) Tumor growth curves of 8 groups mice bearing 4 T_1 xenografts, and (e) the corresponding digital photos of 4 T_1 solid tumors in mice at the end of treatment. Reproduced with permission from Ref. [126], Copyright © 2016, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

demonstrated an excellent sensitivity and a high spatial resolution in detecting tumors.

As noted above, BP nanosheets possess photothermal-conversion properties for PTT application based on their obvious black color. In a recent study, the bulk BP powder was exfoliated into ultrasmall BPQDs (approximately 2.6 nm in lateral size and 1.5 nm in thickness) [130]. After surface PEGylation, the stable BP QDs displayed an excellent NIR photothermal performance, and the photothermal conversion efficiency at 808 nm was 28.4%. Results of *in vitro* experiments indicated that the temperature of BP QDs solution increased rapidly even at a low BP concentration (50 ppm) after NIR irradiation. In another study, Wang et al. [131] synthesized a multifunctional BP-based nanoagent (BP/DTX@PLGA) to achieve targeted PTT/chemotherapy synergistic therapy against cancer metastasis. Both *in vitro* and *in vivo* results confirmed that BP/DTX@PLGA induced apoptosis-dependent cell death and elimination of lung metastasis. This study opened a new way to effectively inhibit tumor metastasis.

In addition, BP can be used for photothermal cancer immunotherapy. Liang et al. [132] successfully developed BPQDs formulation to induce the apoptosis of breast cancer cell *in situ* through NIR irradiation. Meanwhile, it mobilized the immune system to eliminate the residual and metastatic cancer cells. Ye et al. [133] prepared BP-based personalized cancer vaccines (Gel-BPQD-CCNVs) and combined it with PD-1 antibody to prevent tumor relapse and metastasis. Briefly, the BPQD coated with surgically removed tumor cell membrane was loaded into a thermosensitive hydrogel containing GM-CSF and LPS to form Gel-BPQD-CCNVs. After hypodermic injection of Gel-BPQD-CCNVs, GM-CSF was continuously released to recruit dendritic cells (DCs) to capture tumor antigen. Then, under the stimulation of NIR radiation and LPS, DCs entered lymph nodes and expressed antigen to $CD8^+$ T cells, leading to the elimination of metastasis tumor.

3D printing is an emerging technology with great research potential in the field of tissue engineering, and is hailed as the beginning of a new era of biomedical technology. With this advanced technology, a variety of artificial scaffolds were fabricated, ranging from tissue regeneration to cancer treatment and even the creation of artificial organs [134]. Very recently, Yang et al. [135] incorporated BP nanosheets into a 3D printed biological glass (BG) scaffold, constructing an unprecedented 3D printed therapeutic platform. The dual-function BP-BG scaffold thus designed could be used for the effective photothermal treatment of osteosarcoma, which is beneficial to further bone tissue regeneration, and thus effectively overcome the limitations of current osteosarcoma therapy.

The aforementioned paradigms have shown that graphene-based nanomaterials and their analogues can be widely used in the sensing field. Therefore, it is reasonable to consider whether BP nanosheets can also be effectively applied to the biosensing field. As a paradigm, Peng et al. [136] prepared Au nanoparticle-decorated few-layer BP (FL-BP) to detect carcinoembryonic antigen (CEA), which showed a wide detection range from 1 pg/mL to 10 μg/mL and a high sensitivity of 0.20 pg/mL. The high electron-transfer and excellent electron-donor capacity of FL-BP greatly improved the detection sensitivity for cancer biomarker. Therefore, BP-based biosensors have the potential to be used in clinical samples of patients suffering from colon and breast cancer.

Some progresses have been made in overcoming BP's surface instability, including surface protection, surface chemical modification and doping [137]. Surface protection refers to the formation of a protective layer on the BP surface to isolate oxygen and water. For example, Zeng et al. [138] reported a delivery system based on polydopamine (PDA)-modified BP nanosheets to enhance the stability and photothermal performance. Surface chemical modification indicates that lone pair electrons of BP can form coordination bonds, covalent bonds or noncovalent bonds so as not to react with oxygen. For instance, Sun et al. [129] used BPQDs coordinated with TiL_4 as PA imaging contrast agent. The empty orbital of titanium atoms accepted the lone pair electrons of BP to form a ligand band, resulting in an obviously improved stability. In addition, doping other elements such as tellurium (Te) and sulfur (S) into the BP layer could also enhance its stability [139,140], and further in-depth studies are needed.

Overall, BP has gained influential and sustainable status in various biomedical fields like drug delivery, theranostics, tissue engineering and biosensing with its excellent physiochemical properties. BP nanosheets can induce cellular apoptosis by producing intracellular singlet oxygen, although its mechanism is still unclear. This issue deserves the attention from the future biological field, which may further lead to new biological applications. Meanwhile, the methods to improve the stability of BP also need to be further studied.

9. 2D graphitic nitride nanomaterials for biomedical applications

Some nitrogen-based 2D nanomaterials, such as g-C_3N_4, h-BN, do not belong to any of the above categories due to their unique atomic species and arrangement. In general, h-BN alternates boron and nitrogen hetero atoms to form a hexagonal monolayer, while g-C_3N_4 forms a strong and regular structure of alternating carbon and nitrogen atoms [30]. For a long time, researchers have been speculated that these elements can form their own 2D allotropes, and only in recent decades the synthesis has been realized. In the subsequent sections, g-C_3N_4 and h-BN will be introduced separately in the context of biological applications.

9.1. G-C_3N_4

G-C_3N_4 nanosheets have been reported to possess high drug loading capacity. Recently, a targeted and O_2-evolving PDT theranostic platform based on Fe^{III}-doped g-C_3N_4 nanosheets was demonstrated to achieve almost complete tumor ablation [141]. The ultrahigh surface area of g-C_3N_4 nanosheets could achieve the co-loading of mitochondria-targeting agent triphenylphosphonium bromide (TPP) and photosensitizer methylene blue (MB). Doped Fe^{III} endowed the nanosystem with peroxidase-like properties, which could catalyze H_2O_2 to generate O_2, thus overcoming tumor hypoxia and improving PDT efficiency. Unsurprisingly, this work inspires a new direction for the development of g-C_3N_4-based multifunctional nano-reagents for the destruction of tumor.

Like graphene and its derivatives, g-C_3N_4 nanosheets can selectively adsorb DNA molecules and coordinate with protons or metal ions. With this property, several sensitive and unlabeled fluorescent biosensors have been developed based on g-C_3N_4 nanosheets. Xiang et al. [142] developed a novel fluorescent g-C_3N_4 nanosheet biosensor for highly sensitive, unlabeled detection of alkaline phosphatase (ALP) within the detection limit of 0.08 U/L. To put it simply, the high-affinity chelation of pyrophosphate (PPi) with Cu^{2+} could inhibit the coordination of g-C_3N_4 with Cu^{2+}. In the presence of ALP, PPi could be catalyzed into phosphate (Pi) with weak interaction with Cu^{2+}, so as to restore the coordination between Cu^{2+} and the g-C_3N_4 nanosheet, and effectively quench the strong fluorescence of g-C_3N_4 via photoinduced electron transfer (PET), thus achieving the detection of ALP. Hence, such a g-C_3N_4-based biosensor may have great application potential in biomedicine and clinical diagnostics.

In addition, g-C_3N_4 nanosheets have been proved as an effective therapeutic agent and imaging contrast agent due to their inherent photocatalytic and fluorescence properties. Chen et al. [143]

prepared core-shell nanoparticles by encapsulating photosensitizer g-C_3N_4 nanosheets into a zeolitici-midazolate framework-8 (ZIF-8) shell. DOX was further loaded into the ZIF-8 shell for chemotherapy. As a result, combining DOX with the PDT effect of g-C_3N_4 nanosheets significantly improved the therapeutic efficacy, achieving photo-chemo synergetic therapy. Moreover, the fluorescence properties of DOX (red fluorescence) and g-C_3N_4 nanosheets (blue fluorescence) provided additional dual-mode imaging to monitor DOX release and guide cancer treatment process. In another work, Liu et al. [144] synthesized ultrathin g-C_3N_4 in 2D confined region of LDHs (CN/LDHs) via microwave induced condensation reaction between citric acid and urea. The as-prepared CN/LDHs emitted strong cyan light under UV irradiation, with an ultra-high solid-state quantum yield (SSQY) of 95.9%±2.2%, which was the highest among carbon materials. Cell culture experiments showed that such g-C_3N_4-based nanomaterial could be used for up-conversion cell imaging.

9.2. h-BN

Monolayer h-BN, which consists of boron and nitride atoms with the stoichiometry of B and N being 1:1, has aroused extensive

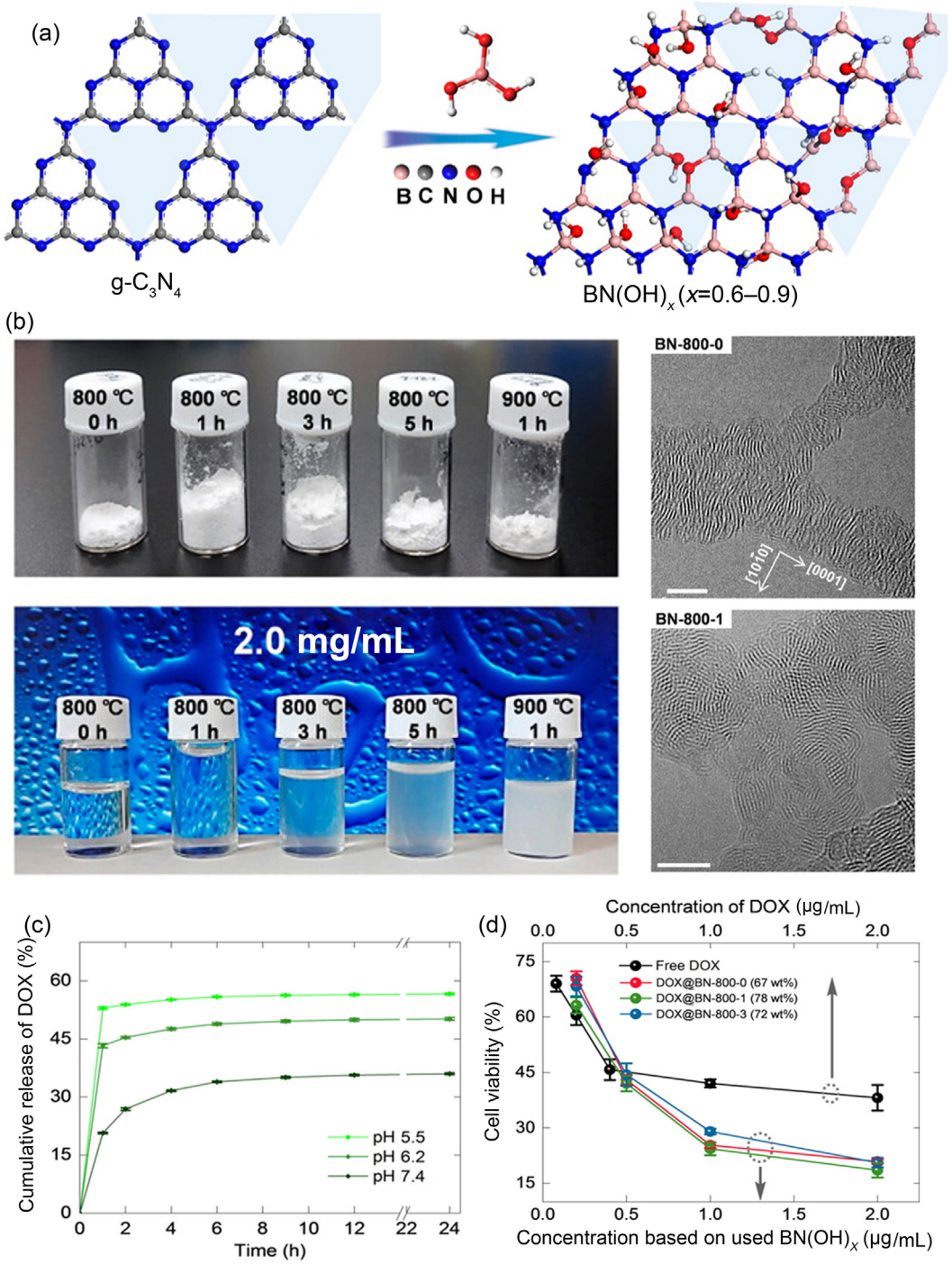

Fig. 10. (Color online) Application of h-BN nanosheets to drug delivery. (a) Schematic illustration of the preparation of h-BN nanosheets. (b) Water-soluble h-BN and corresponding high-resolution TEM (HRTEM) images. (c) Release kinetics of DOX from DOX@BN under pH 5.5, 6.2 and 7.4 conditions. (d) Viability of LNCaP cells in the presence of DOX@BN and free DOX solutions with different concentrations. Reproduced with permission from Ref. [146], Copyright © 2014, American Chemical Society.

research interest from scientists. Different from a single element of graphene-based nanomaterials, the strong polarity of B—N bond localizes the electronic states, giving it unique properties with a large bandgap in especial (5–6 eV) [145]. The chemical inertness, low toxicity, excellent mechanical properties and high thermal conductivity of h-BN make it an ideal candidate for drug delivery and tissue engineering. In this section, the biomedical application of h-BN will be reviewed briefly, although relevant research is still scarce.

2D h-BN nanosheets possess many unique properties including hierarchical porosity and high specific surface area, making them suitable for drug delivery. As an example, Weng et al. [146] produced highly dispersed water-soluble hydroxylated h-BN nanoplates via the thermal substitution of C atoms with boric acid substructures in g-C_3N_4 (Fig. 10). The DOX loading capacity of hydroxylated h-BN materials could reach 309 wt%. The drug release kinetics was monitored, and the results showed that the DOX could be released slowly and stably from the hydroxylated h-BN carrier in the neutral solution, but it was triggered to release rapidly in the acidic aqueous environment. Such novel h-BN based materials possess excellent biocompatibility and perform well in anticancer drug loading, delivery and release, suggesting their promising application in the field of biomedicine.

Considering the strength and biocompatibility of h-BN nanosheets, some scientists have applied them to tissue engineering. For instance, Yoo et al. [147] synthesized an artificial nacre on the basis of functionalized h-BN nanosheets, which could enhance mechanical strength and induce cell differentiation at the same time. Nevertheless, the research on the application of h-BN nanosheets in the tissue engineering filed is almost scarce. Therefore, it is suggested that relevant study should be strengthened in the future.

9.3. Summary of 2D graphitic nitride nanomaterials for biomedical applications

In general, both g-C_3N_4 and h-BN have exhibited remarkable chemical and mechanical properties, indicating their potential application in biology. However, as far as we are concerned, the biomedical application of g-C_3N_4 and h-BN has not been fully studied. At the same time, we should also pay more attention to the innovation of synthesis and functionalization methods of 2D graphitic nitride nanomaterials, so that they can be applied to more fields.

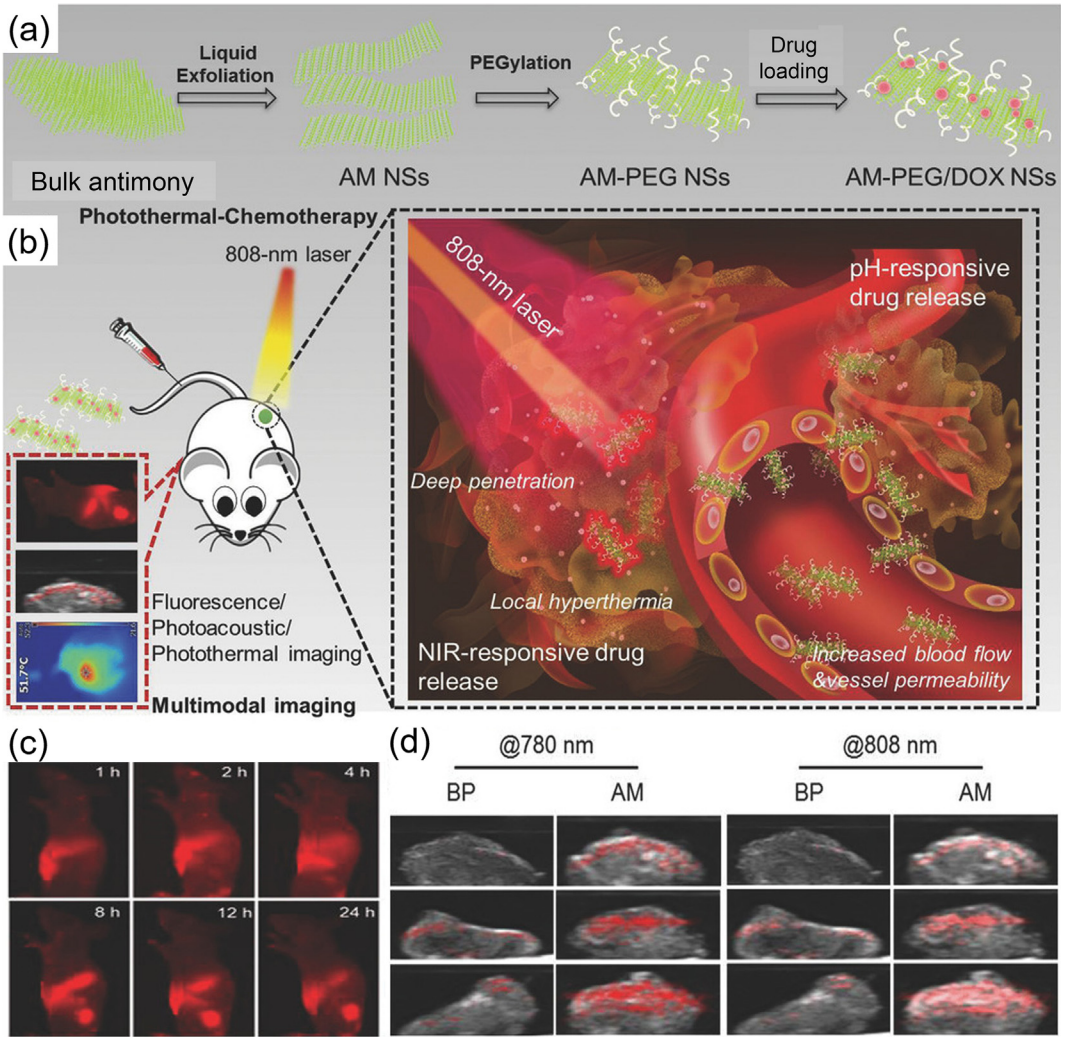

Fig. 11. (Color online) AM for drug delivery and imaging-guided cancer theranostiocs. (a) Schematic illustrations of the preparation of AM-PEG/DOX NSs. (b) The systemic applications of AM-PEG/DOX NSs. (c) *In vivo* fluorescence images of nude mice at different time points. (d) *In vivo* ultrasound and PA images of tumors at wavelengths of 780 and 808 nm. Reproduced with permission from ref. [152], Copyright © 2018, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

10. Other types of 2D nanomaterials for biomedical applications

In addition to the above 2D nanomaterials, several other types such as AM, B NSs, SnTe NSs have been studied in biomedical applications. In brief, AM has attracted broad attention with appropriate band gaps and excellent stability, and its layered structure is similar to BP to some extent [148]. B NSs with single-atom thickness have attracted great interest due to its extraordinarily optical, electronic, thermal and anisotropic mechanical properties [149]. As for SnTe NSs material, it has been considered as an ideal substitute for narrow bandgap nanomaterials with low toxicity and NIR optical activity [150]. In the following part, we will introduce biomedical applications of AM, B NSs and SnTe NSs respectively.

10.1. AM

AM has been reported with excellent photothermal conversion efficacy and can be used as photothermal agents (PTAs) for cancer therapy. For instance, Tao et al. [151] synthesized highly dispersed AM quantum dots (AMQDs) by a simple liquid exfoliation method. The prepared PEG-coated AMQDs showed superior NIR photothermal performance with a photothermal conversion efficiency of 45.5%, and exhibited rapid NIR-induced degradability. This is the first report on AM in biomedicine application. In their another study, a drug-delivery platform (AM-PEG/DOX NSs) based on AM NSs was developed with a high DOX loading capacity of 150% (Fig. 11) [152]. With potential degradability, AM NSs delivery platforms showed pH-/photoresponsive release properties, as well as fluorescence/photoacoustic (PA)/photothermal imaging properties. Moreover, this study revealed that AM-PEG NSs were taken up by MCF-7 cells through macropinocytosis and caveolin-dependent endocytosis pathways, and then transported via "early endosomes"–"late endosomes"–"lysosomes".

In addition, like graphene and BP, AM can be used as SPR biosensor for DNA molecule sensing. Xue et al. [153] developed a biosensor based on AM for specific label-free detection of cancer-associated miRNA-21 and miRNA-155 with a detection limit of 10 aM, which was 2.3–10,000 times superior to the current miRNA sensor. Moreover, AM interacted strongly with ssDNA, representing the highest sensitivity in DNA molecule sensing. Such AM-based biosensor serves as promising biomarker for cancer diagnosis and provided an opportunity to develop lab-on-chip platforms.

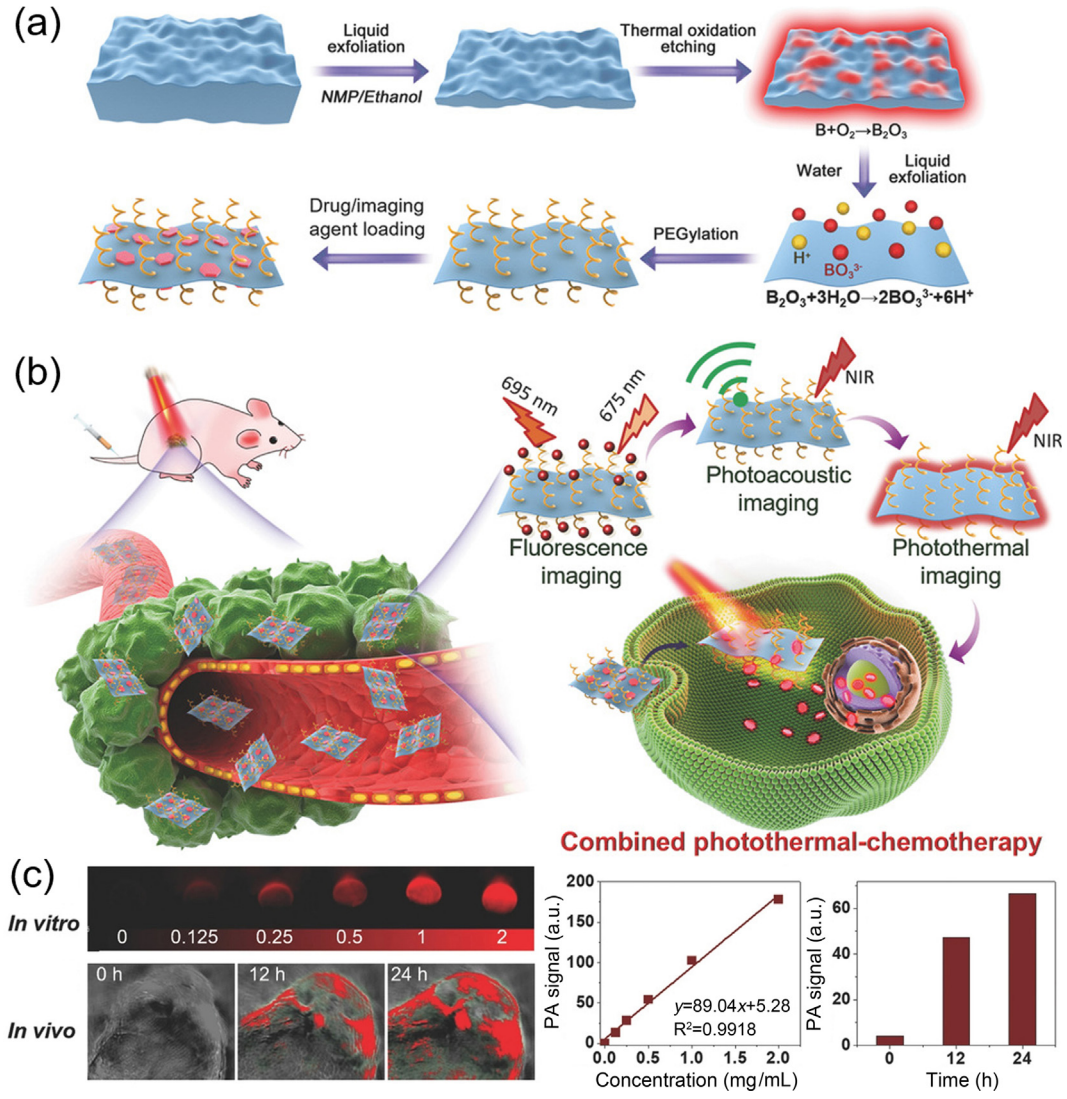

Fig. 12. (Color online) B NSs for multimodal imaging-guided cancer therapy. (a) The Schematic illustration of the preparation of B-PEG/DOX NSs. (b) The scheme of B-based NSs for fluorescence/PA/photothermal imaging-guided synergistic PTT/chemotherapy of cancer. (c) *In vitro* and *in vivo* PA images of B-PEG NSs under different conditions. Reproduced with permission from Ref. [25], Copyright © 2018, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

10.2. B NSs

Ultrathin B NSs are an interesting type of recently developed 2D nanomaterial with high chemical stability, thermoelectricity, superconductivity [154]. Due to these intriguing properties and excellent biocompatibility, B NSs have been explored in nanomedicine. A recent study reported by Ji et al. [25] prepared B NSs through a top-down approach by coupling liquid exfoliating and thermal oxidation etching (Fig. 12). After modifying with PEG-NH_2, both biocompatibility and dispersibility of B NSs were improved with a photothermal conversion efficiency of 42.5%. Moreover, the PEGylated B NSs (B-PEG NSs) achieved a high loading of DOX and imaging agent cyanine5.5 (Cy5.5). As a result, the B-PEG NSs demonstrated synergistic PTT/chemotherapy effect and multimodal fluorescence/PA/photothermal imaging performances.

10.3. SnTe NSs

SnTe NSs are another type of 2D nanomaterial with two essential elements for human. As a semiconductor, SnTe possesses unique cubic crystal structure and the direct bandgap is 0.18 eV at 300 K [63]. Consequently, SnTe NSs are promising to offer NIR optical activity, good biocompatibility, which is suitable for potential diagnosis and cancer treatment. Based on the above features, Zhang et al. [26] successfully developed SnTe NSs-based diagnostic imaging and PTT agent by combining ball-milling and liquid exfoliation methods (Fig. 13). The prepared SnTe NSs were modified with soybean phospholipid (SP) and MnO_2 shell (SnTe@MnO_2-SP NSs), showing excellent stability in physiological environment and unique biodegradability in TME. The photothermal conversion efficiency of SnTe@MnO_2-SP NSs was 38.2% in NIR I and 43.9% in NIR II. In particular, the main degradation product TeO_3^{2-} exhibited

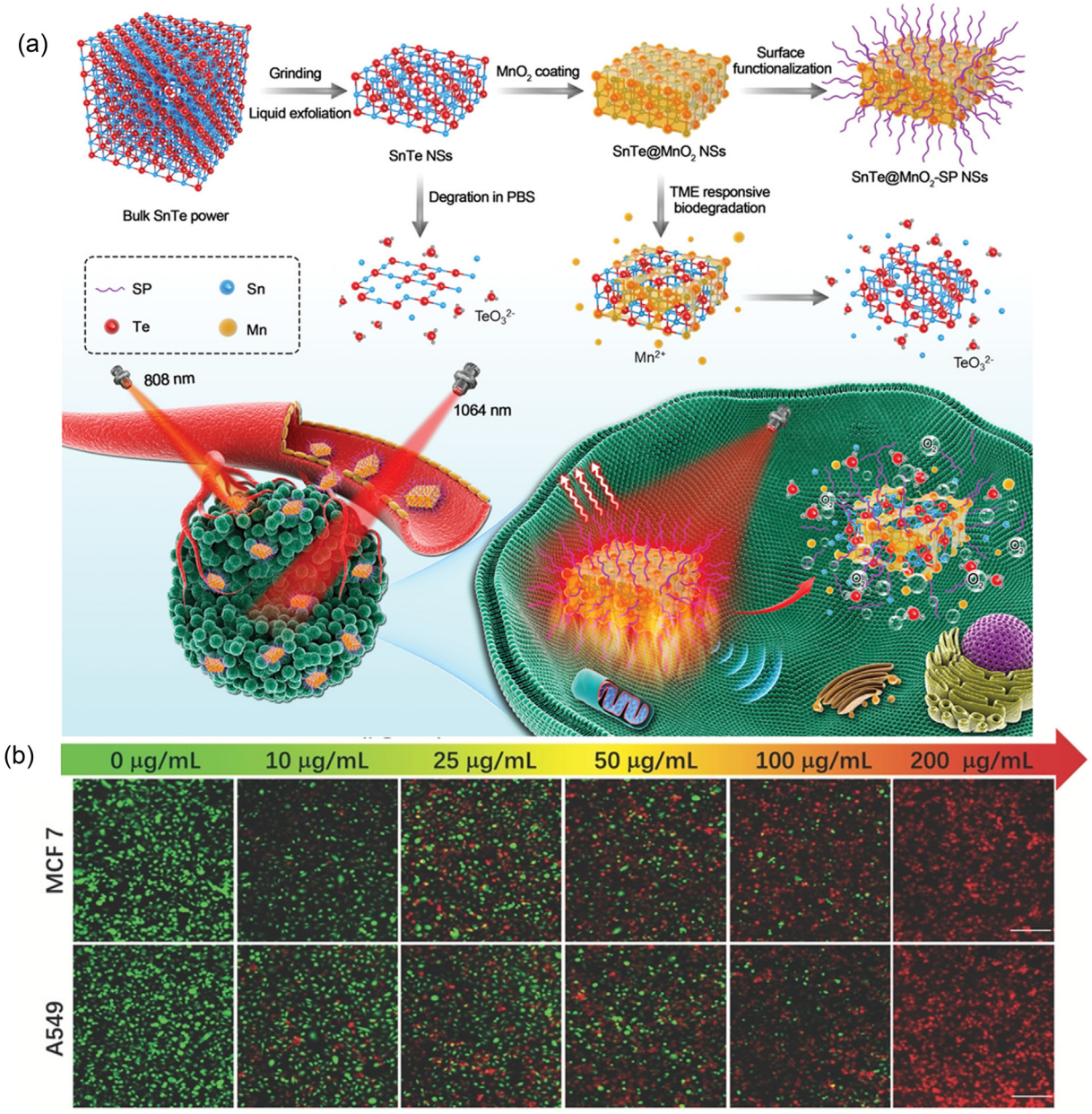

Fig. 13. (Color online) SnTe NSs for cancer theranostiocs. (a) The scheme of SnTe@MnO_2-SP NSs for synergistic PTT/chemotherapy of cancer. (b) CLSM images of MCF7 and A549 cells stained with calcein-AM and PI after incubation with SnTe@MnO_2-SP NSs. Reproduced with permission from Ref. [26], Copyright © 2019, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

excellent chemotherapy effect. Hence, SnTe@MnO_2-SP NSs can be potentially used in synergistic anticancer field.

10.4. Summary of other types of 2D nanomaterials for biomedical applications

All in all, the 2D nanomaterials mentioned above (AM, B NSs, SnTe NSs) are emerging materials in the field of biomedicine and have made some progress in drug delivery and theranostics. However, experimental studies on biosensing, tissue engineering remain largely unexplored, and the synthesis methods mainly focus on the liquid exfoliation method. Therefore, emphasis should be placed on developing new synthesis methods and wide biomedical applications in the future research.

11. Conclusions and outlook

Due to their high surface-to-volume ratios, anisotropic physical and chemical properties, flexible bioactivity and unique structures, 2D nanomaterials are rapidly expanding their biomedical applications. In this review, we have summarized and discussed the most valuable and promising 2D nanomaterials and their progress in drug delivery, combined therapy, biosensors, and tissue engineering. Based on the above studies, the biocompatibility, biodegradability and drug loading of different types of 2D nanomaterials are compared detailedly in Table 1. Graphene-based nanomaterials (graphene, GO, rGO), LDH, TMDs, TMOs and BP remain to be the research focus in the biomedical field. The recently studied g-C_3N_4, h-BN, AM, B NSs and SnTe NSs exhibit promising application prospect, and can be widely evaluated once the synthesis difficulty is overcome. Nevertheless, the investigation of these 2D nanomaterials in biomedicine still stay at the immature stage. Several challenges and issues need to be addressed to facilitate the advances of this field for further clinical translation.

From the perspective of materials, the lack of standard synthetic method to obtain 2D nanosheets with desired structural/compositional parameters such as size, dispersity, charge and quality is a key challenge, because size distribution and morphology are critical factors to determine the therapeutic efficiency and diagnostic performance. With the rapid development of preparation method, the bottom-up method has become an alternative approach to the top-down strategy for obtaining size-uniform nanosheets, although how to produce 2D nanomaterials in large scale remains a big challenge.

It is necessary to further investigate their interactions with biological entities. Understanding the interactions between 2D nanomaterials and structural proteins or genetic materials, as well as how these 2D nanomaterials influence or control various signal pathways, is of critical importance. Such knowledge will deepen our understanding of how the size, shape, chemical composition, and surface characteristics of nanomaterials control specific biological processes. Although the endocytosis pathways and biological activities of 2D BP-PEG and AM-PEG nanosheets in cancer cells have been reported, the exploration is still at a preliminary stage, and more efforts are needed to further study BP, AM and other 2D nanomaterials.

In a variety of studies, 2D nanomaterials can combine with many other biocompatible components to achieve multiple diagnostic and therapeutic purposes. In other words, synergistic treatment can be realized by integrating different therapeutic modalities. However, it is worth noting that the performance of each function may be impaired when multiple functions are integrated into a theranostics system. As the stability of such nanosystems depends on various experimental conditions, further clinical transformation requires a more rigorous and complex biosafety assessment. Therefore, the nanosystem complexities (the loading proportion of drug or imaging agents, degree of aggregations, nonspecific binding, and the loss of biological activity upon transition from *in vitro* to *in vivo*) should be taken into account when setting up nanosystems, and a standard protocol should be established to balance the functional performance and complexity.

While 2D nanomaterials have made great progress, detailed biological and biosafety assessments of them are urgently required to guarantee safety in further clinical translations. Although previous studies have shown that most 2D nanomaterials have good biocompatibility, the supporting data are not convincing enough to prove their safety at the clinical stage. The evaluation should further focus on how 2D nanomaterials affect the human immune system and whether they can be degraded and/or cleared from the body, as well as the degradation mechanism in the body. Moreover, some 2D nanomaterials such as BP are easily degraded, resulting in poor stability and unsatisfactory treatment effect. Therefore, appropriate balance is required to modulate therapeutic efficacy and biodegradability. In addition, current animal models should

Table 1
Comparison of biocompatibility, biodegradability, drug loading capacity of 2D nanomaterials.

2D nanomaterials	Biocompatibility	Biodegradability	Drug loading capacity
GO	100 μg/mL in MDA-MB-231 cells for 48 h; cells viability: 80% [79]		DOX loading: 150% [156]
LDHs	500 μg/mL in HeLa, U87mg, KB and HepG2 cells for 24 h; cells viability: over 90% [100]		SN38 loading: 925% [101] DOX&ICG loading: 797.36%; DOX loading: 344.56%; ICG loading: 227.88% [100]
BP	200 μg/mL in 4 T_1, HeLa, L929, and A549 cells for 24 h; cells viability: over 95% [126]	Degradation during 24 h in PBS [157]	DOX loading: 950% [126]
g-C_3N_4	100 μg/mL in A549 cells for 24 h; cells viability: 90% [143]		DOX loading: 93% [155]
AM	200 μg/mL in HEK 293, HeLa, PC3, MCF7, and A549 cells for 24 h; cells viability: over 80% [151]	Degradation within 1 h upon NIR laser [151]	DOX loading: 150% [152]
PVP-coated Fe_3S_4 TNSs	200 μg/mL in HeLa cells for 24 and 72 h; cells viability: over 80% [111]		
MnO_2	200 μg/mL in MDA-MB-231 cells for 48 h; cells viability: 80% [117]		
B NSs	500 μg/mL in HeLa, PC3, MCF7, and A549 cells for 48 h; cells viability: over 90% [25]		DOX loading: 114% [25]
SnTe NSs		Degradation after 5 h in PBS [26]	
h-BN			DOX loading: 309% [146]
MoS_2			DOX loading: 239%; SN38 loading: 118%, Ce6 loading: 39% [107]
rGO			DOX loading: 98% [82]

not be limited to mice, and should be further extended to larger animals. Further clinical trials should be carried out only after proving the biosafety of 2D nanomaterials.

There are also some challenges to overcome before practical biomedical applications. In terms of drug delivery, the biocompatibility of 2D nanomaterials is a key factor. Some 2D nanomaterials with excellent biocompatibility, such as LDHs that can be taken orally, should be considered for their ion toxicity and metabolism in the body. For tissue engineering, in general, 2D nanomaterials are combined with polymers to form scaffolds, so consideration needs to be given to whether the polymers used are toxic, and whether the 2D nanomaterials are slowly released from the scaffolds within the acceptable range of the human body. As for biosensors, the 2D nanomaterials studied at present are basically used for *in vitro* biosensing. Therefore, it is necessary to improve the uniformity and stability of 2D nanomaterials, as well as the accuracy, sensitivity and repeatability of detection. In the case of cancer theranostics, the current studies mainly adopt intravenous injection to deliver the theranostic agents into the body. Thus, it is worth considering the stability of 2D nanomaterial in the blood. Moreover, whether the dosage and metabolism of 2D nanomaterials in the body can cause obvious toxicity should be noticed. Therefore, after a thorough consideration and suitable resolution on these issues, practical biomedical applications of 2D nanomaterials in drug delivery and tissue engineering would realize in the near future.

Overall, 2D nanomaterials provide unprecedented opportunities and challenges for the development of next-generation technologies in cell biology, medical diagnostics, tissue engineering, cancer treatment, biosensing, drug and gene delivery. It is worth believing that 2D nanomaterials will expand the field of biomedicine. Hoping that in the near future, 2D nanomaterials will enter the stage of clinical research and application.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (20601010, 21671013, 21521005, 81871786, 81611130091, and 81702113), the Beijing Natural Science Foundation (2174082), and the Fundamental Research Funds for the Central Universities (buctylkxj01, XK1802-6).

Author contributions

Ruizheng Liang and Min Wei conceived the review topic. Tingting Hu wrote the manuscript in consultation with all the other authors. Xuan Mei and Yingjie Wang arranged all the figures. Xisheng Weng, Ruizheng Liang and Min Wei modified the manuscript. All authors contributed to the final manuscript.

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