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Design, Synthesis, and Surface Modification of Materials Based on Transition-Metal Dichalcogenides for Biomedical Applications

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With the rapid development of nanotechnology, the emerging transition-metal dichalcogenides (TMDCs) have become one of the most promising inorganic nanomaterials for medical applications due to their distinctive structures and properties. TMDCs with different sizes and morphologies exhibit unique structural advantages, as well as versatile properties. However, concerning their practicability for biomedical applications, routes toward their synthesis and chemical/physical functionalization for biosystem applications must be identified. Herein, recent advances in the design, synthesis, and surface modification of TMDC-based nanomaterials specific for biomedical applications are reviewed. First, the basic consideration regarding how to fabricate biocompatible TMDCs efficiently for biomedical use is discussed. Solution-based synthesis methods for 2D TMDCs, as well as TMDC-based nanocomposites are then summarized. In addition, general strategies applied for surface functionalization of TMDCs are also discussed. Finally, current challenges and future perspectives for these promising materials in biosystem applications are outlined.

1. Introduction

The development of transition-metal dichalcogenides (TMDCs) has remained a hot research topic over the last few decades.[1–7] TMDCs, with the generalized formula of MX_2, where M refers to a transitional metal typically from groups 4–10 (Ti, Nb, Ta, Mo, or W) of the periodic table and X is a chalcogen atom (S, Se, or Te), have been reported to possess diverse properties varying from insulating (e.g., HfS_2) and semiconducting (e.g., MoS_2 and WS_2) to semimetallic (e.g., WTe_2 and $TiSe_2$) as well as true metallic (e.g., NbS_2 and VSe_2).[8] Thus, they are widely used in many fields such as the hydrogen-evolution reaction, energy storage, transistors, optoelectronics, sensors, catalysis, and biomedicine.[9–16] In particular, owing to their relatively low cytotoxicity as well as their unique structural and chemical/physical properties, TMDCs have been shown to be good candidates for applications in biomedicine, such as multimodal bioimaging, drug delivery, synergistic therapy, and biosensors.[17,18]

The interatomic interactions within bulk TMDC layers are covalent in nature, and the layers are held together by weak van der Waals forces. These features allow them to be easily thinned down to a few layers with only three atoms in one layer, thus exhibiting true 2D properties.[19] The absence of dangling bonds on the surface of TMDCs makes them remain highly stable in liquid and air, which facilitates their incorporation in biosystems.[10] Due to their 2D structure, TMDCs exhibit an extremely large surface-to-volume ratio, making them easy to functionalize and interact with biomedical materials to realize enhanced biocompatibility, as well as the loading of various therapeutic agents.[19,20] In addition to their unique structures, with the combination of chalcogen atoms and transition-metal atoms, TMDCs also exhibit diverse chemistry and physics characteristics, such as optical properties, electronic band structure, Raman scattering, luminescence, and semiconducting behavior.[21] For example, based on their electronic band structure, TMDCs such as MoS_2, WS_2, and TiS_2 show strong optical absorption in the near-infrared (NIR) region and display high photothermal conversion efficiency, which makes them an ideal photoacoustic (PA) imaging contrast agent, as well as a photothermal therapy (PTT) agent in cancer theranostics.[22,23] Moreover, some TMDCs that contain high-atomic-number elements, such as tungsten, also have potential in computed tomography (CT) imaging and radiotherapy (RT) enhancement, due to their capability of attenuating X-rays.[24] To date, TMDCs have shown good capabilities for deep-tissue and live animal imaging (PA/CT imaging) with high spatial resolution, as well as the release of heat-generated therapeutic agents with lower laser power densities.[25,26] In addition, it is known

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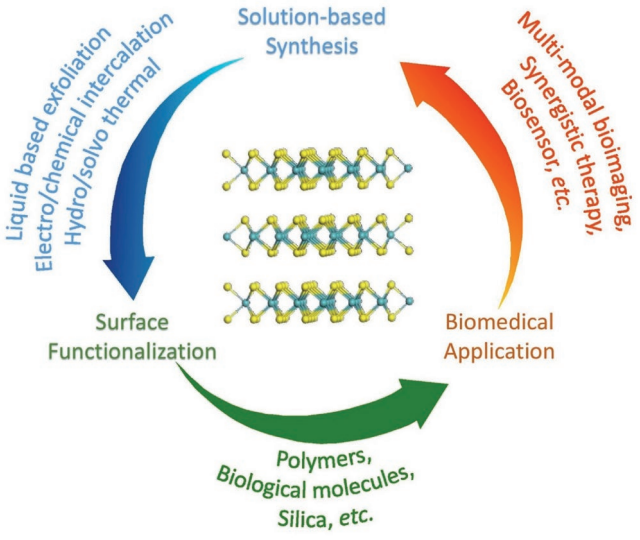
that, by decreasing the particle size, the electronic bandgap and photoluminescence of TMDCs would correspondingly increase, which enables them to be applied in optical cellular observations as well as biosensors.[27–30] For instance, ion-intercalated MoS_2 can be used in cell-viability investigations, based on its photoluminescence.[28] Finally, TMDCs may also be combined with other functional materials to form nanocomposites, which can optimize their performance, and even novel properties can be exhibited for practical use.[2,31,32] For example, the combination of iron oxide with TMDCs can exhibit both the advantages of TMDCs in drug loading, strong NIR and X-ray absorbance, and the magnetic targeting ability of iron oxide, to perform multimodal imaging and combined therapy in cancer treatment.[33,34]

With such distinctive and favorable chemical/physical characteristics, extensive studies have been carried out to explore their applications in the biomedical field. 2D TMDC nanosheets (NSs), as novel inorganic analogs of graphene, are the first developed and most widely studied nanostructure with regard to TMDCs. Moreover, inspired by the exciting discovery and great success of 2D TMDC nanostructures, the research interests of the basic structures and properties originating from other counterparts of TMDCs, such as 0D structure, 3D structure, and even TMDC nanocomposites, have also grown significantly. With TMDCs being introduced into biomedical applications, the kinds of theranostics have been greatly broadened. However, TMDCs are intrinsically water insoluble, which greatly limits their application in biosystems.[35] Generally, the transformation of hydrophobic TMDCs to hydrophilic materials can be done through appropriate solution-based synthesis routes to reduce their hydrophobicity, or by appropriate surface modification, to introduce an additional biocompatible molecular basis to their surface and thus render them water soluble (**Scheme 1**). Therefore, to this end, we present a brief review of the design and fabrication of TMDCs with different dimensions or TMDC-based nanocomposites specifically for biomedical applications. We begin with an overview of the general design principles of



Scheme 1. Overview of the synthesis and surface functionalization of materials based on transition-metal dichalcogenides for biomedical applications.

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TMDCs in biosystem applications (Section 2). The current synthetic routes and surface-modification techniques to prepare different kinds of TMDCs and to incorporate them into biological systems are summarized in Sections 3 and 4. To close, the limits of the aforementioned synthesis and functionalization techniques related to the biomedical applications of TMDCs are discussed. We aim to introduce researchers to the general

principles of the design, synthesis, and functionalization of diverse TMDCs in biomedical applications, so as to inspire more exciting developments in these promising materials.

2. Design Principle of TMDCs for Biomedical Application

Typically, TMDCs are 2D in nature, and they consist of a monolayer of transition-metal atoms sandwiched between two layers of chalcogen atoms in a hexagonal pattern. As shown in **Figure 1**, the transition metals (groups 4–10) and chalcogen atoms (S, Se, and Te) in the TMDCs are highlighted with different colors.[8] With the multiple combinations of different transition-metal atoms with chalcogen atoms, there are roughly 40 known TMDCs, with diverse chemical/physical properties that are apt for biomedical applications, due to their distinct photoluminescence, optical absorption, and direct bandgap.[21] Generally, TMDCs are inherently thin, flexible, strong, and exhibit distinguished higher structural rigidity compared to other 2D nanomaterials.[17] Taken together, these properties make TMDCs suitable for biomedical applications.

However, TMDC materials are not intrinsically hydrophilic, which greatly limits their application in biosystems. Considering biosystem conditions, ideal biomedically used TMDCs should have the following features:

i) Low toxicity: The toxicity profile is the first factor of concern when applying nanoparticles into biological applications. It is reported that TMDCs exhibit lower cytotoxicity than many other nanostructures, such as graphene or Au,[36,37] which makes them potentially valuable for biological applications. However, among TMDC nanomaterials, there are still some elements that are not suitable to be applied in the biomaterial field. For example, tellurium is not suitable for biomedical applications, as it is regarded as a toxic and nonessential element.[38] Consequently, when designing TMDCs for biomedical use, the toxicity should be reduced in order to avoid adverse side effects in vivo.

ii) Good dispersibility, high physiological stability and biocompatibility: For biomedical applications, TMDC nanomaterials enter the body and come into contact with tissue and cells directly; thus, being water soluble, dispersible, and relatively biosystem stable is the basis for their biodistribution and medical function.[39] In addition, to reduce or avoid undesired local or systemic toxicity effects, biocompatibility is another crucial concern for TMDCs to optimize their theranostic performance in biomedical applications.

iii) Relatively small or ultrasmall average particle size (desirably less than 100 nm): It is believed that, under a certain size, nanoparticles can be easily extravasated from the blood pool into tumor tissues due to the altered anatomy of the tumor vessels, and be retained as a result of poor lymphatic drainage, which enables the achievement of an enhanced permeability and retention effect near tumor tissues, and thus delivers a large amount of the theranostic agent to tumors in comparison with normal tissues.[40] Moreover, when the core diameter decreases to the ultrasmall range, renal excretion can be realized, which can further minimize the toxicity of the nanoparticles.[41] Therefore, TMDCs with a small size can increase their in vivo biodistribution as well as efficient theranostic outcomes, which is highly required for biological applications.

Consequently, over the past decade, great efforts have been focused on producing suitable TMDCs in order to meet the abovementioned requirements for biological applications, which can be generally realized in two ways: direct synthetic strategies and additional functionalization methods.

Diverse techniques are available to synthesize different TMDC nanostructures, such as the top-down method (e.g., intercalation and exfoliation) or the bottom-up strategy (hydrothermal or solvothermal method). However, in order to obtain water-soluble TMDCs for biomedical applications, the synthesis process is usually performed in solution, with the assistance of mechanical forces or additional stabilizer/surfactant. **Table 1** shows the solution-based synthesis methods for TMDCs with

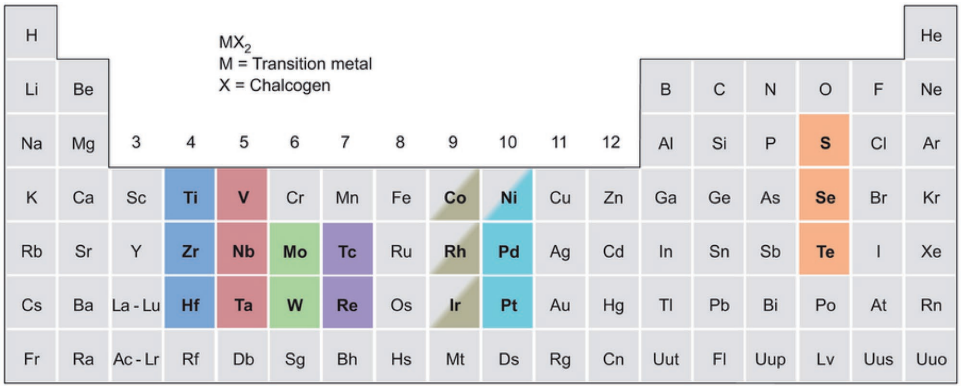

Figure 1. About 40 different layered TMDC compounds exist. The transition metals and the three chalcogen elements that predominantly crystallize in those layered structure are highlighted in the periodic table. Partial highlights for Co, Rh, Ir, and Ni indicate that only some of the dichalcogenides form layered structures. For example, NiS_2 is found to have an apyrite structure but $NiTe_2$ is a layered compound. Reproduced with permission.[8] Copyright 2013, Nature Publishing Group.

Table 1. Summary of the different solution-phase synthesis methods for TMDC-based nanomaterials, including two dimensions (2D), zero dimensions (0D), three dimensions (3D), and TMDC nanocomposites.

Dimensions	Synthesis methods	Subsynthesis methods	Materials	Ref.
2D	Liquid-based exfoliation and intercalation method	Solvent-assisted exfoliation	MoS_2, WS_2, $MoSe_2$, $MoTe_2$, $TaSe_2$, $NbSe_2$, $NiTe_2$	[44–47]
		Surfactant/stabilizer-assisted exfoliation	MoS_2, WS_2, $TaSe_2$, $MoTe_2$, $MoSe_2$, $NbSe_2$, WSe_2,	[48–51]
		Chemical intercalation and exfoliation	MoS_2, WS_2, TiS_2, TaS_2, NbS_2, $TiSe_2$, $NbSe_2$, $MoSe_2$	[52–54]
		Electrochemical intercalation and exfoliation	MoS_2, TaS_2, TiS_2, WS_2, ZrS_2, $NbSe_2$, WSe_2	[55,56]
	Wet-chemical method	Hydro/solvothermal method	TiS_2, WS_2, MoS_2, ReS_2	[23,24,57,58]
0D	Liquid-based intercalation and exfoliation method	Sonication-assisted exfoliation	MoS_2, ReS_2, TaS_2, WS_2, $MoSe_2$, WSe_2 $NbSe_2$ quantum dots	[59–61]
		Chemical intercalation and exfoliation		[62–64]
	Wet-chemical method	Hydro/solvothermal method	MoS_2, WS_2 quantum dots	[65–67]
3D	Wet-chemical method	Hydrothermal method	MoS_2 nanoflowers, MoS_2 hollow spheres	[68–70]
TMDC nanocomposites	Wet-chemical method	Hydro/solvothermal method	Flower-like CdS–MoS_2, MoS_2–Bi_2S_3, MoS_2–Fe_3O_4, WS_2–Fe_3O_4	[32,33,71,72]

different dimensions, as well as TMDC-based nanocomposites. Generally, the choice of the synthesis method depends on the specific function that the TMDCs will perform. In addition, factors such as cost, environmental-friendliness, scale-up production, number of layers, thickness, and size, as well as the dimensions of the TMDCs should also be taken into consideration while choosing appropriate synthesis strategies.

Surface modification is another essential route to fabricate TMDCs for biomedical applications. Various modifying materials, such as polymers, proteins, or small organic molecules, have been applied to render TMDCs with water-soluble ability through either physical absorption or chemical conjunction (**Figure 2**). The basic principle for functionalization of TMDCs is that the functionalities should be biocompatible, of low toxicity, and even be able to impart TMDC nanomaterials with bioactive properties. In general, surface modification can not only imbue TMDCs with solubility in water, but also endow them with additional biomedical abilities, such as multimodal imaging, drug/gene delivery (loading capability), and synergistic therapy in cancer theranostics. For example, some semiconductive polymers can help TMDCs realize amplified photoacoustic signals in PA imaging;[42] inorganic mesoporous silica offers an easy platform for mass drug loading;[43] or functionalized TMDCs carrying photosensitizers can achieve a photodynamic–photothermal synergistic therapy.[44] In addition to endowing TMDCs with high biocompatibility and the ability of loading of theranostic agents, the functionalization process can also render them with better biological performance, such as improved cellular uptake and biodistribution, or prolonged circulation time in the blood, to realize an enhanced efficiency of diagnostic and therapeutic output.

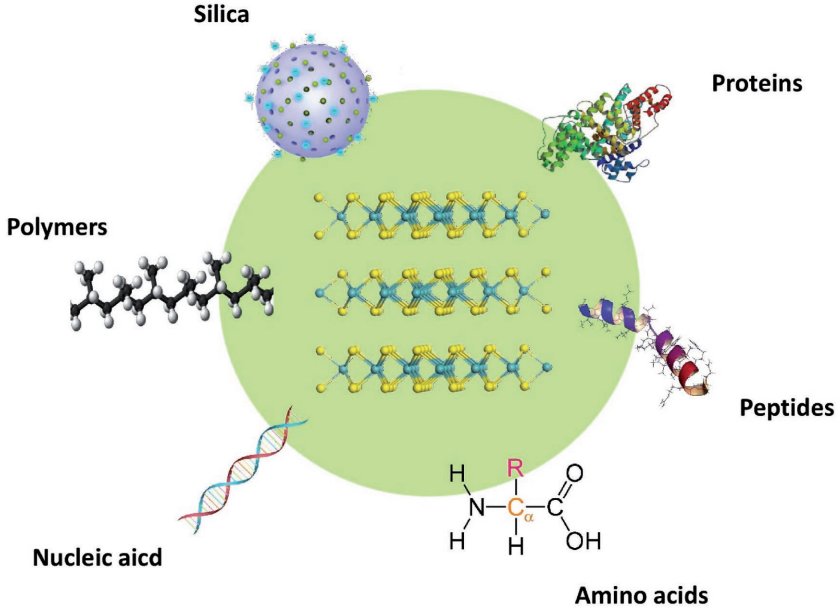

Figure 2. Mostly used functional materials such as polymers, biomolecules, and silica in the functionalization of TMDCs for biomedical purposes.

3. Solution-Based Synthesis of TMDCs

3.1. Layered (2D) TMDC Synthesis

Graphene-like 2D layered TMDC is the most widely studied TMDC nanostructure in biomedical applications due to its large surface and low cytotoxicity, as well as superior physical and chemical properties.[5,6,10,17,19] Up to now, a series of methods have been developed to synthesize 2D TMDC nanosheets. Among all the reported methods, traditional routes such as micromechanical cleavage and chemical vapor deposition are not suitable

for biological applications, especially for in vivo theranostic purposes, because the as-prepared TMDCs are usually large-sized and water insoluble.[18,73] Liquid-based techniques, on the other hand, hold enormous promise as convenient and cost-effective approaches toward the mass production of safe, handleable, and applicable small-sized 2D TMDCs.[73–78] Generally, liquid-based synthesis methods can be divided into liquid-based exfoliation/intercalation methods (top-down methods) and wet-chemical synthesis methods (bottom-up methods). Liquid-based exfoliation and intercalation methods include solvent-assisted exfoliation and stabilizer/dispersant-assisted exfoliation, as well as chemical or electrochemical intercalation and exfoliation. Wet-chemical synthesis methods mainly include hydrothermal and solvothermal methods.

3.1.1. The Liquid-Based Exfoliation Method

Solvent-Assisted Exfoliation: Methods of particular relevance to solvent-assisted exfoliation generally involve ultrasound or shear forces to break the interlayer interactions of the 2D TMDCs. The affinity between the host materials and solvents weakens the interaction of the constituent layers of the bulk solid, and the separation of sheets can be achieved by subsequent sonication. Direct liquid-based exfoliation was first proposed by Coleman et al. in 2011.[45] They demonstrated that bulk TMDC crystals, such as MoS_2, WS_2, $MoSe_2$, $MoTe_2$, $TaSe_2$, $NbSe_2$, and $NiTe_2$, can be efficiently exfoliated into ultrathin nanosheets by direct sonication in many common solvents. Among the applicable solvents, *N*-methyl-pyrrolidone (NMP) and isopropyl alcohol are the most promising solvents to minimize the energy of exfoliation. Since then, an enormous amount of research has been carried out to exfoliate 2D TMDCs in different solvents. More recently, Zhao and co-workers developed a simple and efficient strategy to synthesize MoS_2 nanosheets via an improved oleum-treated liquid exfoliation.[25,44] In this process, grinding, milling, and high temperature were applied to facilitate the isolation of MoS_2 nanosheets for further functionalization. In 2016, a mild liquid-phase exfoliation (other than ultrasonication, a mild bath sonication) method to produce luminescent suspensions of MoS_2 and WS_2 in *N*-methylpyrrolidone was reported.[46] The resulting ultrathin nanosheets were further verified to be able to be transferred in water and stay safe in human breast cancer cells, which paves their way in biological applications. In addition, to exfoliate TMDC materials in organic solvents, water can also be used as a solvent to disperse the nanosheets. For example, Forsberg et al. introduced a method to directly disperse MoS_2 in water using mechanical and liquid exfoliation.[47] It should be mentioned that the concentration achieved by this method is only half of the concentration realized by liquid exfoliation in organic solvents under the same liquid-exfoliation conditions. Nevertheless, this method is still a promising exfoliation strategy because of its environmental friendliness and good dispersion stability.

Surfactant/Stabilizer-Assisted Exfoliation: Single-layered TMDC nanosheets can also be exfoliated from the parent bulk materials using ultrasonication in selected solutions with the assistance of surfactants or stabilizers. As TMDCs are intrinsically hydrophobic in their pristine form, applying certain stabilizers or surfactants can help TMDC's direct exfoliation and subsequent dispersion in water.[35] It should be noted that additional surfactants or stabilizers may not only facilitate the exfoliation process, but also allow the simultaneous functionalization of the corresponding nanomaterials. Such functionalization can endow these 2D TMDC nanomaterials with high stability under physiological conditions, which is very essential for further applications in biological systems.[79] Over the past years, a variety of ionic surfactants,[48,80] polymers,[50,81,82] and biomolecules[51,83,84] have been successfully employed to assist the exfoliation of TMDCs.

In addition, Coleman and co-workers developed an ultrasonication-assisted liquid-exfoliation method to produce few-layered TMDCs from bulk crystals directly in water by the use of ionic surfactants, such as sodium cholate.[48,85] Additionally, other than using ultrasonication during the exfoliation process, 2D TMDCs can also be obtained by exposing bulk crystals to a shear force (kitchen blender) and/or a compression-force treatment (ball milling) in aqueous ionic-surfactant solutions, such as aqueous sodium dodecyl sulfate solution.[49,80] These processes can lead to well-dispersed surfactant-coated flakes with a size of only a few hundred nanometers, showing great potential for further applications. Recently, a facile poly(vinylpyrrolidone) (PVP)-assisted exfoliation method was utilized to simultaneously exfoliate and noncovalently modify $MoSe_2$ nanosheets.[50] The hydrophilic PVP-coated $MoSe_2$ nanosheets were proved to have high photothermal conversion efficiency and good biocompatibility, to serve as efficient PTT agents.

To further broaden the bioapplicability of 2D TMDCs obtained by liquid-based exfoliation, natural stabilizers, typically biomolecules, instead of man-made ones, have been widely explored over the past few years. For instance, bovine serum albumin (BSA) has been extensively used to exfoliate bulk TMDCs into nanosheets in many studies.[51,86,87] This method can simultaneously synthesize and functionalize TMDC nanosheets with high stability in water and good biocompatibility, which enables TMDCs to be applied further as good photothermal agents in cancer treatment. Here we provide a state-of-the-art summary of specific biorelated compounds (such as BSA, cellulose, chitosan, and amino acid) that have been used as dispersants for 2D TMDC exfoliation (shown in **Table 2**). By exfoliating with biomolecules, TMDC materials can be endowed with an amphiphilic character, naturally leading to their implementation in biomedical applications (e.g., biosensing, drug delivery, and multimodal cancer therapy).

Chemical Intercalation and Exfoliation: Chemical intercalation and exfoliation of layered bulk crystals in liquid are another of the most developed strategies to synthesize 2D TMDCs for biomedical applications. Due to the specific layered structure and weak van der Waals forces between the layers, host materials can be intercalated by molecules or ions facilitated by sonication or other appropriate means.[97] Among all the intercalatable materials, alkali metals, such as lithium, sodium, and potassium, have been intensively explored in the intercalation of bulk TMDC crystals.[52,53,98–103] In a typical Li-intercalation experiment, bulk TMDC powders are mixed with *n*-butyllithium in hexane under an inert gas (i.e., nitrogen) atmosphere, and subsequent exfoliation in water is realized by (ultra)sonication

Table 2. Summary of the different biomolecules that have been reported in the literature to exfoliate and colloidally disperse 2D TMDCs.

Biomolecule	2D TMDCs	Exfoliation method	Ref.
Bovine serum albumin	MoS_2, WSe_2, WS_2	Bath/tip sonication	[51,86–88]
Gelatin	MoS_2, WS_2	Bath sonication	[89]
DNA/RNA	WS_2, WSe_2	Bath sonication	[83,90]
Cellulose	MoS_2	Bath sonication	[91]
Chitosan	MoS_2	Bath sonication/ionic-liquid-assisted grinding	[92–94]
Tannic acid	MoS_2	Bath sonication	[95]
Hyaluronic acid	MoS_2	Probe sonication	[96]
Amino acid	MoS_2	Bath sonication	[84]

treatment (**Figure 3**). Notably, the H_2 gas generated from the exfoliation process (between lithium and water) can also help to push the adjacent TMDC layers apart. Nevertheless, a study regarding the toxicity assessment of MoS_2 nanomaterials has revealed that *n*-butyllithium- and *tert*-butyllithium-exfoliated MoS_2 nanosheets are more cytotoxic than methyllithium-exfoliated MoS_2,[104] which further gives us a hint to choose the best intercalating agent for application in biosystems. Apart from alkali metals, intercalation can also be implemented using small molecules.[103] Rajamathi and co-workers once replaced lithium-intercalated Li_xMS_2 (M = Mo and W) with NH_3/NH_4^+, and, assisted with subsequent sonication, obtained stable MS_2 dispersions.[54] One advantage of this method is that the evolution of ammonia gas during sonication would assist the subsequent exfoliation process, and the gas would finally escape from the dispersion by heating. While MS_2 obtained from Li intercalation may be contaminated by lithium compounds such as LiOH, which requires further extensive cleaning to get rid of these impurities, the as-prepared ammoniated MS_2 shows great stability and dispersibility in various solvents including water, which indicates its potential application in biomedical use.

Electrochemical Intercalation and Exfoliation: Although traditional chemical lithium intercalation is one of the widely used techniques for 2D TMDC synthesis, its rigid and complex reaction requirements (oxygen- and water-free environment) and long reaction time (3 d), as well as the hard-to-control intercalation extent, have restricted it from practical application. Recently, Zhang and co-workers developed a controllable and effective electrochemical lithium-intercalation approach to produce monolayered 2D TMDCs.[55,56] As shown in **Figure 4**, the layered bulk TMDC materials were incorporated as a cathode, and the lithium foil was used as an anode in an electrochemical setup, where the lithium intercalation in these materials could be monitored and well controlled during the discharge process to avoid insufficient or overwhelmed Li intercalation. With subsequent ultrasonication and exfoliation of the intercalated compounds in water or ethanol, well-dispersed nanosheets were finally obtained. This method is convenient since it can be easily conducted at room temperature within 6 h. Up to now, most single- and few-layered TMDC nanosheets, such as MoS_2, TaS_2, TiS_2, WS_2, ZrS_2, $NbSe_2$, and WSe_2, have been successfully prepared in a high yield and large scale by using this method. A similar electrochemical method was also applied to intercalate sodium ions in the layers of MoS_2.[105] TMDC nanosheets synthesized by this method are potentially suitable for biomedical use because they can be directly dissolved in water with good stability and easily be modified with functional materials.

3.1.2. The Wet-Chemical Synthesis Method

In contrast to liquid-based exfoliation, which is a top-down method, the wet-chemical synthesis method is a typical bottom-up process to synthesize TMDC nanosheets with desired size and thickness. It generally relies on the chemical reaction of metal salts as precursors to prepare TMDC nanosheets.[106] The hydrothermal method is an example of the wet-chemical synthesis method, where the reaction is realized in a sealed autoclave at elevated temperature (to 220 °C) under an inert gas atmosphere (**Figure 5**).[107] As a representative example, Shi and co-workers used $(NH_4)_2MoS_4$ as a precursor for the one-pot synthesis of sized-controllable PEGylated MoS_2 nanosheets in PEG-400 aqueous solution, which further shows potential as a drug-delivery system, as well as a PTT agent for cancer treatment.[57] The

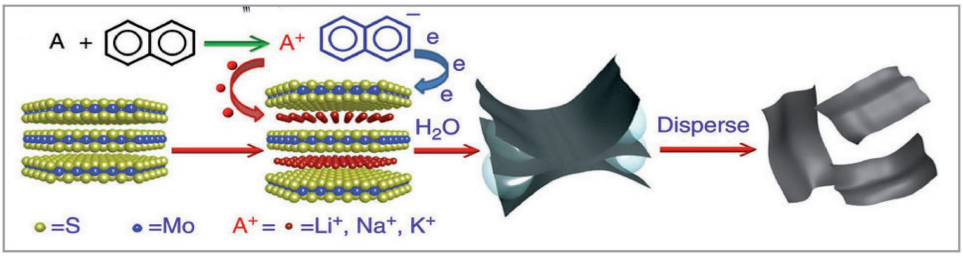

Figure 3. Schematic of the metal-ion intercalation process. Pre-exfoliated MoS_2 reacts with $A^+C_{10}H_8^-$ to form an intercalation sample, and then exfoliates to single-layered sheets in water. Reproduced with permission.[53] Copyright 2014, Nature Publishing Group.

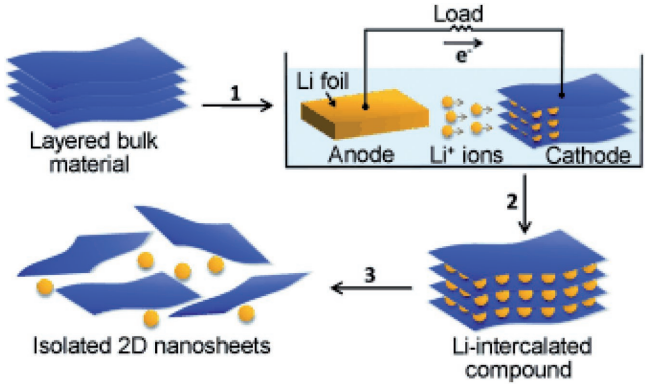

Figure 4. The electrochemical lithiation process for the fabrication of 2D nanosheets from the layered bulk material. Reproduced with permission.[55] Copyright 2011, Wiley-VCH.

PEG-400 chains used in the process can efficiently anchor on the surface of the nanosheets, which can help in the formation of nanosheets with particular controlled size, as well as endow MoS_2 nanosheets with enhanced colloidal stability and biocompatibility.

The solvothermal method is another typical wet-chemical synthetic strategy. Different from the hydrothermal method, organic solvents, instead of water, are used as the reaction medium in a sealed vessel, where the reaction temperature is higher than the boiling point of the solvent. As the temperature reaches above the boiling point of the solvent system, the nanocrystal-synthesized reaction can be promoted automatically under high pressure. This method is also widely used to prepare 2D TMDC nanomaterials that can be adapted to biomedical applications.[18,58,108] Recently, Liu and co-workers successfully synthesized functionalized metal-ion-doped TiS_2 and WS_2 for cancer therapy.[23,24] In their typical experiment, a quick reaction of the transitional metal (M) chloride and oleylamine (OM) was realized to form M—OM ligands, and then TMDC nanosheets were obtained by the subsequent addition of sulfur powder. In 2017, the uniform ultrathin rhenium disulfide (ReS_2) nanosheets, synthesized through the solvothermal method using $NaReO_4$ and S in oleylamine, were reported by Shen et al.[58] The as-prepared ReS_2 nanosheets with further poly(ethylene glycol) (PEG) functionalization showed strong NIR light absorption and high X-ray attenuation, as well as low toxicity in vivo, which suggests their applications in image-guided photothermal therapy and radiotherapy.

There is still no appropriate synthetic procedure to prepare TMDC nanosheets with scale-up production by the hydro/solvothermal method due to its rigid reaction conditions, such as high temperature and pressure. However, it is expected that various 2D TMDCs with controllable and desirable structural as well as physical/chemical properties could be obtained by this method because of its controllable nature through varying different experimental parameters.[18]

3.2. Synthesis of 0D TMDC

0D TMDC nanostructures possess distinct structure and edge chemistry, which are different from 2D morphologies. 0D TMDCs, such as TMDC quantum dots (QDs), have been recognized as a prospective candidate for biomedical applications, due to their high stability, low toxicity, large edge-to-volume ratios, photoluminescence, and suitable optical properties.[4,20] In particular, most 0D TMDCs reported to date are ultrasmall. This advantage is extremely useful in terms of cell uptake and renal clearance for in vivo applications, which not only enhances their therapeutic effects but also avoids side effects due to their efficient clearance through kidney excretion.[26,109] Similar to the synthesis of 2D nanosheets, synthesis methods for 0D TMDC nanodots can also be divided into the

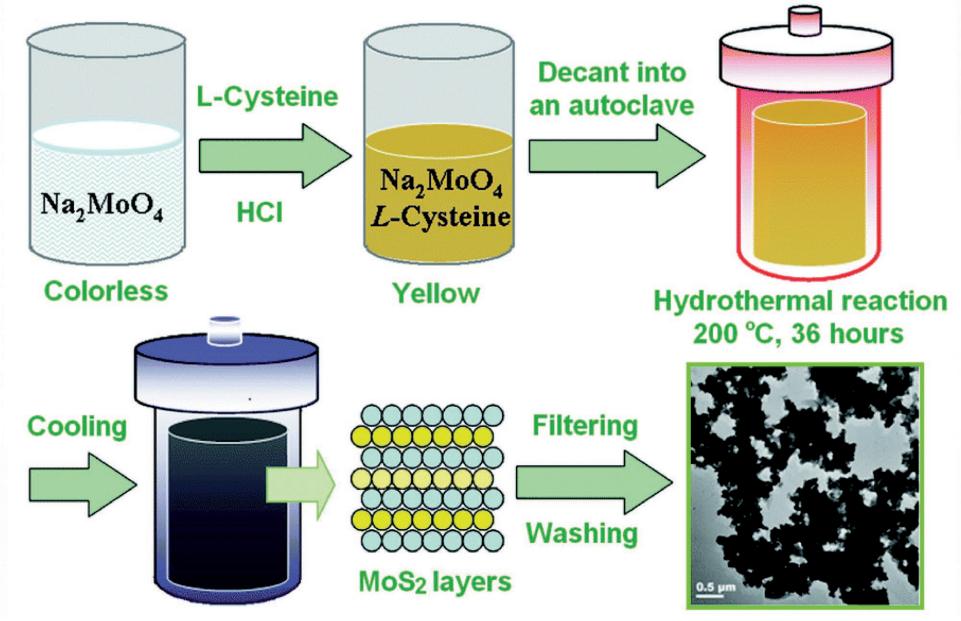

Figure 5. Preparation of MoS_2 by a simple hydrothermal method. Reproduced with permission.[107] Copyright 2014, Royal Society of Chemistry.

liquid-based intercalation/exfoliation method and the wet-chemical synthesis method.

3.2.1. Liquid-Based Intercalation and Exfoliation

The liquid-based intercalation and exfoliation method (the top-down approach) includes solution-based exfoliation and chemical (ion) intercalation–exfoliation. Sonication-assisted exfoliation in a liquid phase is the most widely used technique for preparation of 0D TMDCs.[110–114] For example, highly catalytic MoS_2 nanodots were synthesized in *N,N*-dimethylformamide solution with the assistance of ultrasonication from bulk MoS_2 powders.[59] With the combination of sonication and grinding techniques, TMDC QDs (MoS_2, ReS_2, TaS_2, WS_2, $MoSe_2$, and WSe_2) and $NbSe_2$ nanodots (**Figure 6**a) can also be obtained by solution-based exfoliation.[60,61] Similar to sonication-assisted exfoliation, pulsed laser ablation was also developed to synthesize biocompatible fullerene-like MoS_2 nanoparticles from bulk powder by Wu et al.[115] This green and convenient process can be carried out directly in water, and additional cell studies also demonstrated the good solubility and biocompatibility of the newly synthesized nanoparticles, which paves their way to various biomedical applications.

The chemical intercalation–exfoliation method is also broadly used for the synthesis of 0D TMDCs in biomedical application. For example, alkali metals, such as lithium, sodium, and potassium, have been intensively explored in the intercalation of bulk TMDC crystals.[62,63,116,117] Allwood and co-workers once successfully synthesized luminescent monolayered WS_2 QDs as a nontoxic fluorescent label for high-contrast bioimaging applications through a potassium-ion-intercalation process.[62] More recently, a sodium-ion-intercalation-assisted approach for large-scale preparation of MoS_2 QDs was introduced by Zhou et al.[63] The as-prepared MoS_2 QDs obtained by sodium-ion exfoliation exhibited strong fluorescence, high photostability, and low cytotoxicity, and can serve as a fluorescent probe for long-term live-cell tracing. It can be also envisioned that other TMDC QDs, such as WS_2 and $MoSe_2$, with different fluorescent emissions could be synthesized by a similar protocol. Additionally, a sulfuric-acid-assisted intercalation–ultrasonic route for the preparation of TMDC QDs from bulk powders was also introduced in many studies (Figure 6b).[26,64,114]

3.2.2. The Wet-Chemical Synthesis Method

The wet-chemical synthesis method (bottom-up method) for the preparation of 0D TMDCs for biomedical applications can also be classified into hydrothermal and solvothermal methods. Among the established chemical methods, the hydrothermal method has attracted extensive interest due to its obvious advantages, such as precise control, ease of handling, high yield, low air pollution, and uniform products.[20] Like 2D TMDCs, the hydrothermal synthesis of 0D TDMCs is carried out in a sealed poly(tetrafluoroethylene) (Teflon) autoclave with a reaction temperature of around 200 °C using metal salts as precursors.[118] For example, a one-step hydrothermal route was used to synthesize water-soluble MoS_2 QDs using $(NH_4)_2MoS_4$ as a precursor, where the size of the QDs can be very easily confined by controlling the chemical reaction conditions.[65] Additionally, TMDC QDs can also be obtained through the hydrothermal route from bulk powder. In 2016, Xian and co-workers reported a combination of ultrasonication and a hydrothermal route to successfully synthesize WS_2 QDs from WS_2 powders using hexadecyltrimethylammonium bromide (CTAB) as a surfactant.[66] This strategy might be suitable for synthesis of other TMDC QDs, and the subsequent water-soluble QDs are expected to have great potential applications in biological systems.

Similar to the hydrothermal method, the solvothermal method is also performed in a Teflon-lined autoclave kept at over 100 °C. A range of solvothermal approaches from various

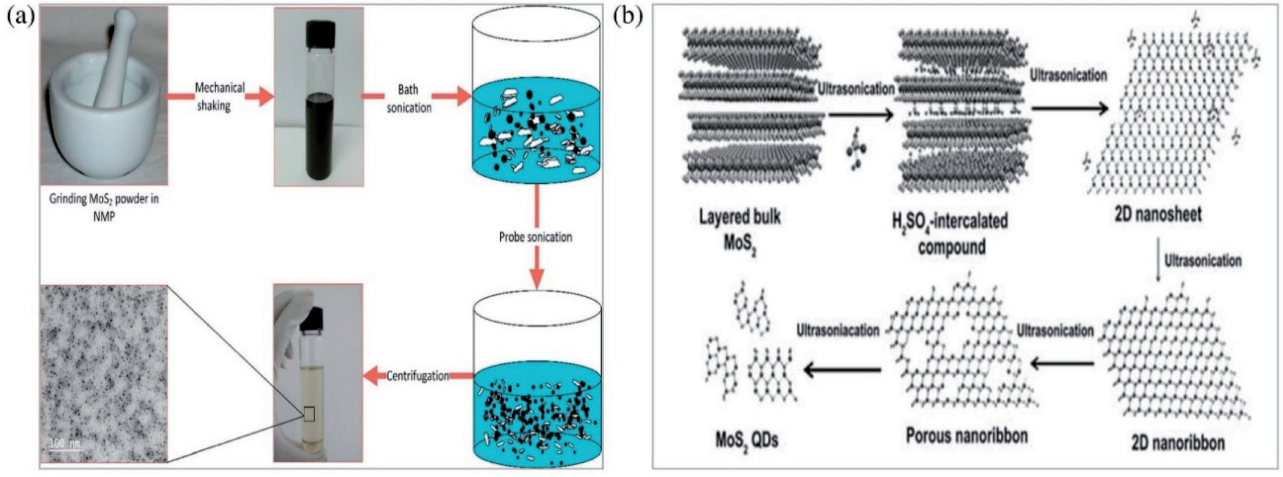

Figure 6. a) Schematic diagram for the synthesis of MoS_2 quantum dots (QDs) consisting of wet grinding in NMP followed by mechanical shaking for 4 h, bath sonication for 4 h, probe sonication for 1 h, and centrifugation at 8000 rpm for 30 min. Reproduced with permission.[61] Copyright 2016, Elsevier. b) Schematic representation of the H_2SO_4 intercalation mechanism for preparing MoS_2 QDs. Reproduced with permission.[64] Copyright 2015, Wiley-VCH.

precursors have been utilized for preparation of 0D TMDCs. For example, Gu et al. reported a facile and one-step ethanol thermal synthesis of MoS_2 QDs from MoS_2 powder.[67] The as-prepared MoS_2 QDs exhibited small size, high dispersibility, low cytotoxicity, and excellent photostability, and are expected to be promising probes for application in biological and deep-tissue imaging. Additionally, TMDC QDs can also be synthesized from metal salts in organic solutions. Liu et al. reported a one-step solvothermal method for synthesis of ultrasmall MoS_2 nanodots by the decomposition of $(NH_4)_2MoS_4$ using methanol as a basic solution.[109] The nanodots were further modified with glutathione (GSH) (total size is still under 10 nm), which exhibits efficient tumor homing/treatment abilities and rapid body-clearance behavior, making them a promising candidate for cancer theranostics without long-term toxicity concerns.

What is more, a facile colloidal chemical route designed by Lin et al. can be also classified in this section, as it requires chemical reaction under high temperature.[119] In a typical experiment, MoS_2 QDs were obtained using $(NH_4)_2MoS_4$ as a precursor and oleylamine as a reducing agent. The as-prepared MoS_2 QDs were further confirmed to be photoluminescent, and could be applied as a probe for real-time optical cellular imaging.

3.3. Synthesis of 3D TMDCs

Creating 3D TMDC nanostructures, such as flower-like microspheres or hollow spheres, is of high fascination for their applications in nanomedicine. They possess distinct features that other dimensional nanostructures do not have. For example, layered MoS_2 hollow spheres (LMHSs) can be envisioned as rolled-up MoS_2 layers forming a spherical structure. More strain-related defects may occur, as a result of the curving layered structure, which may change their electronic properties and UV–vis–NIR absorption characteristics.[70] Most 3D TMDC nanostructures are prepared via hydrothermal processes.[68,69,120–124] For example, Zhao and co-workers reported a one-pot synthesis of PEG-modified MoS_2 nanoflowers through the hydrothermal strategy using $H_{24}Mo_7N_6O_{24}\cdot 4H_2O$ as a precursor.[68] This PEG–MoS_2 nanoflowers were shown to function as a biocompatible antibacterial system for convenient, rapid, and effective wound disinfection. More recently, Wang et al. reported albumin-functionalized flower-like MoS_2 nanoparticles through a facile hydrothermal procedure using $Na_2MoO_4\cdot 2H_2O$ and CH_4N_2S as precursors (**Figure 7**a).[69] These functionalized hybrid nanoparticles exhibited high biocompatibility and low toxicity, as well as good microwave-susceptive properties, and can be used as microwave-hyperthermia-susceptible agents for in vivo cancer therapy. In 2016, Meng and co-workers successfully synthesized LMHSs using $Na_2MoO_4\cdot 2H_2O$ and $(NH_2)_2CS$ as reactants (Figure 7b).[70] Due to their curving layered hollow spherical structure, the newly synthesized LMHSs exhibit unique electronic properties, as well as strong NIR absorption and high photothermal conversion efficiency. Both in vitro and in vivo studies demonstrated their excellent PTT efficacy for cells and tumors under the guidance of digital subtraction angiography, computed tomography, and thermal imaging, providing a new route to cancer theranostic application.

3.4. Synthesis of TMDC Nanocomposites

As dimensional TMDC nanostructures have received tremendous attention and showed great promise in biomedicine, the

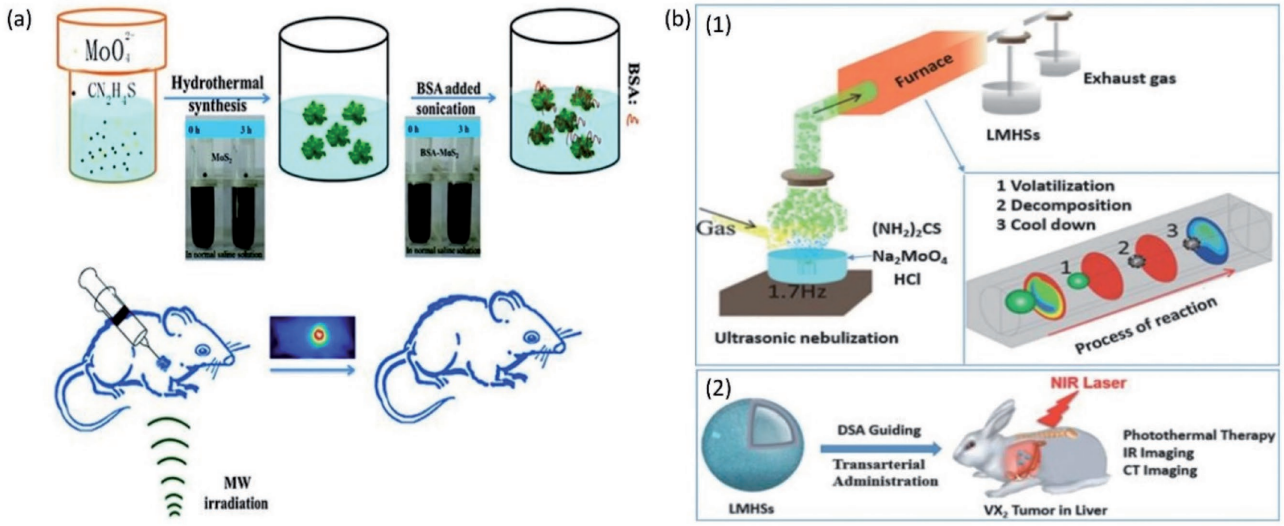

Figure 7. a) Schematic illustration of the synthesis process of BSA–MoS_2 nanoflowers as nanoagents for efficient cancer microwave thermal (MW) therapy. Reproduced with permission.[69] Copyright 2016, Royal Society of Chemistry. b-1) The synthesis scheme of layered MoS_2 hollow spheres (LMHSs) prepared by the chemical aerosol flow method. b-2) A schematic illustration of NIR photothermal therapy in a rabbit liver VX_2 tumor model via transarterial administration. DSA: Digital subtraction angiography. b) Reproduced with permission.[70] Copyright 2016, Wiley-VCH.

study of TMDC-based composites is therefore attracting the interest of more and more researchers. Combining TMDCs with other materials is useful, as the newly synthesized nanocomposites have the advantages of their components, and they may also generate new functions due to synergistic interactions between the two different materials. Thus, studying the synthesis of TMDC-based nanocomposites is useful for exploring novel functionalized composite materials. TMDC-based nanocomposites are mostly synthesized by wet-chemical methods (the hydrothermal or solvothermal synthesis method). For example, flower-like CdS–MoS_2 nanocomposites were prepared via a simple one-pot hydrothermal method using $CdCl_2$ and Na_2MoO_4 as precursors.[71] The combination of CdS with MoS_2 exhibits an improved electro-chemiluminescence property, photocatalytic activity, biocompatibility, and better photoresponsivity, and was applied to the determination of immunoglobulin E (IgE) in human-serum samples. Additionally, a facile one-pot solvothermal synthesis of MoS_2/Bi_2S_3 composite using $(NH_4)_2MoS_4$ and $Bi(NO_3)_3\cdot 5H_2O$ as precursors was reported by Wang et al. in 2015 (**Figure 8**a).[32] Owing to the high NIR absorption of MoS_2 and strong X-ray attenuation ability of Bi_2S_3, this nanocomposite could be applied not only as a PTT agent and a PA contrast agent, but also as a radiosensitizer and a CT contrast agent for multimodality tumor imaging and therapy.

In addition to using one-pot synthesis methods, multistep methods can also be employed to prepare TMDC nanocomposites with greatly improved performance. For example, many TMDC nanocomposites, such as MoS_2/Fe_3O_4,[72,125] $WS_2@Fe_3O_4$,[33] and iron-oxide-coated MoS_2 nanocomposites,[34] have been prepared by multistep methods. TMDC nanoflakes have an advantage of efficient molecular binding and drug loading, as well as strong NIR and X-ray absorbance, while Fe_3O_4 possesses a good magnetic targeting ability. Therefore, such hybrid nanocomposites are able to exhibit multimodal imaging and synergistic therapy for cancer treatment. For example, MoS_2/Fe_3O_4 nanotheranostics synthesized by a two-step hydrothermal route were reported by Zhao and co-workers.[72] PEG–MoS_2 nanoflakes were first mixed with $FeCl_3$ under ultrasonication, and then hydrazine hydrate was added to facilitate the synthesis reaction under 180 °C in a sealed autoclave. In another study by Liu and co-workers, a magnetic $WS_2@Fe_3O_4$ nanocomposite was obtained by first synthesizing WS_2 nanosheets through the Li-intercalation method, and then ultrasmall superparamagnetic iron oxide nanoparticles were synthesized from $Fe(acac)_3$ with the functionalization of meso-2,3-dimercaptosuccinic acid (DMSA). Finally the WS_2 nanosheets and DMSA-modified IONPs were mixed together under ultrasonication and stirring.[33] The as-obtained MoS_2/Fe_3O_4 and $WS_2@Fe_3O_4$ composites both showed high stability and low toxicity in biosystems, and possess great potential for multimodal-imaging-guided combination therapy of cancer.

In another typical example, Han et al. reported a composite of MoS_2 and upconversion nanoparticles (UCNPs) through a multistep method.[126] MoS_2 was first obtained using oleum-assisted exfoliation following chitosan functionalization. Carboxyl-modified $NaYF_4$:Yb, Er UCNPs were synthesized through a simple thermal-decomposition method using YCl_3, $YbCl_3$, and $ErCl_3$ as precursors. The MoS_2–UCNPs composites were obtained in an aqueous solution of 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS), and subsequently modified with folic acid (FA). This MoS_2–UCNPs–FA was then loaded with phthalocyanine (ZnPc), which integrated the multifunctions of photodynamic therapy, PTT, and upconversion luminescence imaging into one nanoplatform for efficient cancer therapy with less side effects (Figure 8b).

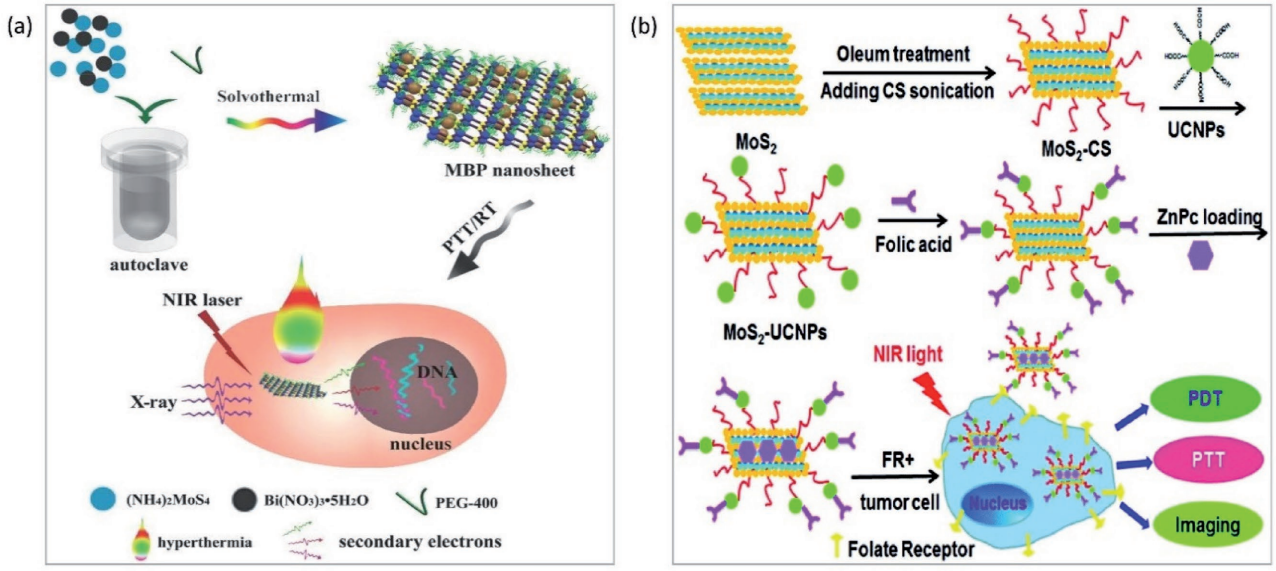

Figure 8. a) Schematic illustration of solvothermal synthesis of MoS_2/Bi_2S_3–PEG (MBP) nanosheets and tumor photothermal therapy (PTT) and radiotherapy (RT). Reproduced with permission.[32] Copyright 2015, Wiley-VCH. b) Schematic illustration of the fabrication process of MoS_2–UCNPs–folic acid/phthalocyanine (FA/ZnPc) and the simultaneous imaging-guided cancer theranostic application. FR: Folate receptor, PDT: Photodynamic therapy. Reproduced with permission.[126] Copyright 2016, Royal Society of Chemistry.

4. Functionalization of TMDC

As mentioned above, some TMDC synthesis methods have been developed to endow TMDCs with water-soluble properties. However, most TMDCs synthesized through traditional methods are not biocompatible or cannot stay stable in a physiological environment, which hinders their future biological use.[50,127] Surface functionalization is thus an efficient and critical step to fabricate TMDCs for various biomedical applications. In addition, to render TMDCs with hydrophilic properties, surface modification can also exert a great impact on their biological performance, such as improved cellular uptake and biodistribution and prolonged circulation time in the blood, as well as stabilized performance in a complex biomedium (e.g., plasma or cellular binding receptors).[128–130] Due to their large surface-to-volume ratio, it is easy to integrate TMDCs with other functional components to enrich their characteristics for various biomedical purposes, such as drug delivery, synergistic therapy, multimodal imaging, or highly sensitive biosensing.[125,127,131] Such a large surface area also affords maximal interaction with the targeting site, so as to increase diagnostic sensitivity as well as therapeutic efficiency. Generally, surface functionalization of TMDCs can be realized through physical adsorption and chemical functionalization.

Noncovalent physical absorption to modify TMDCs is performed when retaining the basic properties of TMDCs is necessary, or removing the functional groups from the TMDCs is part of the functioning mechanism for biomedical applications.[5,19] In general, functional organic or inorganic components can be physically absorbed onto the surface of TMDCs through hydrophobic interactions,[23] electrostatic attraction,[25] and van der Waals forces.[132,133] In contrast, compared with physical absorption, chemical modification of TMDCs involves the formation of tight chemical bonds between the organic functional materials and the surface of the TMDCs, which are relatively strong and can enable modified TMDCs to stay more stable in complicated physiological environments.[5,134,135] During the past few years, various organic/inorganic molecules, such as polymers or silica, have been used to functionalize the surface of TMDCs either via physical absorption or chemical attachments, to change both the physical and chemical properties. In this section, we will give a brief introduction of the most used functional materials as examples for the review of the functionalization of TMDCs for biomedical purposes.

4.1. Polymers

Biocompatible polymers are the most widely used functional materials, and they can be modified to the TMDC surface through either chemical functionalization or physical absorption. Typically, in a chemical way, functionalization of TMDCs is achieved either by ligand conjugation of sulfur atoms from functional materials at sulfur-vacancy sites or through a covalent disulfide bond/coordination interaction between the functional group and the surface sulfur (or Se or Te in other TMDCs).[136–138] It has been reported that, during a drastic intercalation exfoliation process, some of the sulfur atoms may be lost from the surface of a TMDC nanosheet, leaving defects available for binding with sulfur-terminated molecules.[139,140] Liu et al. have therefore tested a sulfur-terminated PEG-based polymer, especially lipoic-acid-terminated poly(ethylene glycol) (LA-PEG), to modify different TMDCs, such as MoS_2 nanosheets,[100,141] WS_2 nanosheets,[142] WS_2 QDs,[26] and flower-like MoS_2,[122] as well as MoS_2–iron oxide nanocomposites.[34] They found that these LA-PEG-modified TMDC materials all exhibit desirable compatibility in a physiological environment with additional excellent biomedical applications, such as multimodal imaging and synergistic therapy for cancer treatment. In addition to PEG, other polymers such as poly(acrylic acid) (PAA),[143] polyethylenimine (PEI),[144] combined PAA–PEG[145] or PEI–PEG,[131,146] or polyaniline (PANI),[130] as well as generation-5 poly(amidoamine) dendrimers–lipoic acid (G5-LA)[147] are also widely used in the process for functionalization of TMDCs. For example, similar to LA-PEG functionalization, effective polymer conjugation via the disulfide bond was reported by Kim et al., in which MoS_2 was modified with LA-modified PEI, as well as thiolated PEG polymers (MoS_2–PEI–PEG) (**Figure 9**a).[131] This MoS_2–PEI–PEG nanocomposite was demonstrated to be highly biostable and displayed low toxicity in cells, which provides a spatiotemporally controllable and effective platform to deliver gene materials into cells. Additionally, G5-LA-modified MoS_2 via the disulfide bonds was presented by Kong et al., and it was shown to have good colloidal stability, excellent photothermal conversion efficiency, and photothermal stability.[147] It was further verified that these G5-LA–MoS_2 nanoflakes were able to deliver Bcl-2 siRNA to cancer cells based on the dendrimer amines on the surface, as the dendrimer amines with positive surface potential can deliver negatively charged siRNA through electrostatic interactions. In this way, in the end, it was proposed that the synthesized G5-LA–MoS_2 nanoflakes might be a potential nanoplatform for combinational gene silencing and PTT of cancer. Apart from disulfide-bond functionalization of TMDCs, PANI-modified MoS_2 QD nanohybrids were reported by Wang et al.[130] These MoS_2@PANI nanoparticles are terminated with −COOH groups, which can be conjugated with PEG–NH_2 by stable amide bonds, to form soluble and stable MoS_2@PANI nanohybrids (Figure 9b). Further in vivo and in vitro studies have demonstrated that this newly synthesized nanohybrid might have the potential to realize dual-modal imaging (PA/CT) and synergistic PTT/RT simultaneously in anticancer study.

In addition to chemical conjugation, polymers can be also modified onto TMDCs by physical absorption, generally during the synthesis process. For example, PEG or PEG-based copolymers have been applied to modify various TMDC nanostructures through physical absorption, such as MoS_2 nanosheets,[42] TiS_2 nanosheets,[23] ReS_2 nanosheets,[58] and WS_2 nanoflakes,[24,129] as well as flower-like MoS_2.[68] The outer hydrophilic part of the amphiphilic polymers (such as PEG-grafted poly(maleic anhydride-*alt*-1-octadecene) (C_{18}PMH–PEG)) attached onto the TMDCs leads to their aqueous dispersion and further bioapplication. As has been reported, PEG-modified TMDCs, modified by physical absorption, exhibit high stability in physiological solutions and no appreciable in vitro toxicity, and have been further verified to serve as multi-bioimaging and synergistic cancer therapy agents. In 2014, Zhao and co-workers successfully modified MoS_2 with

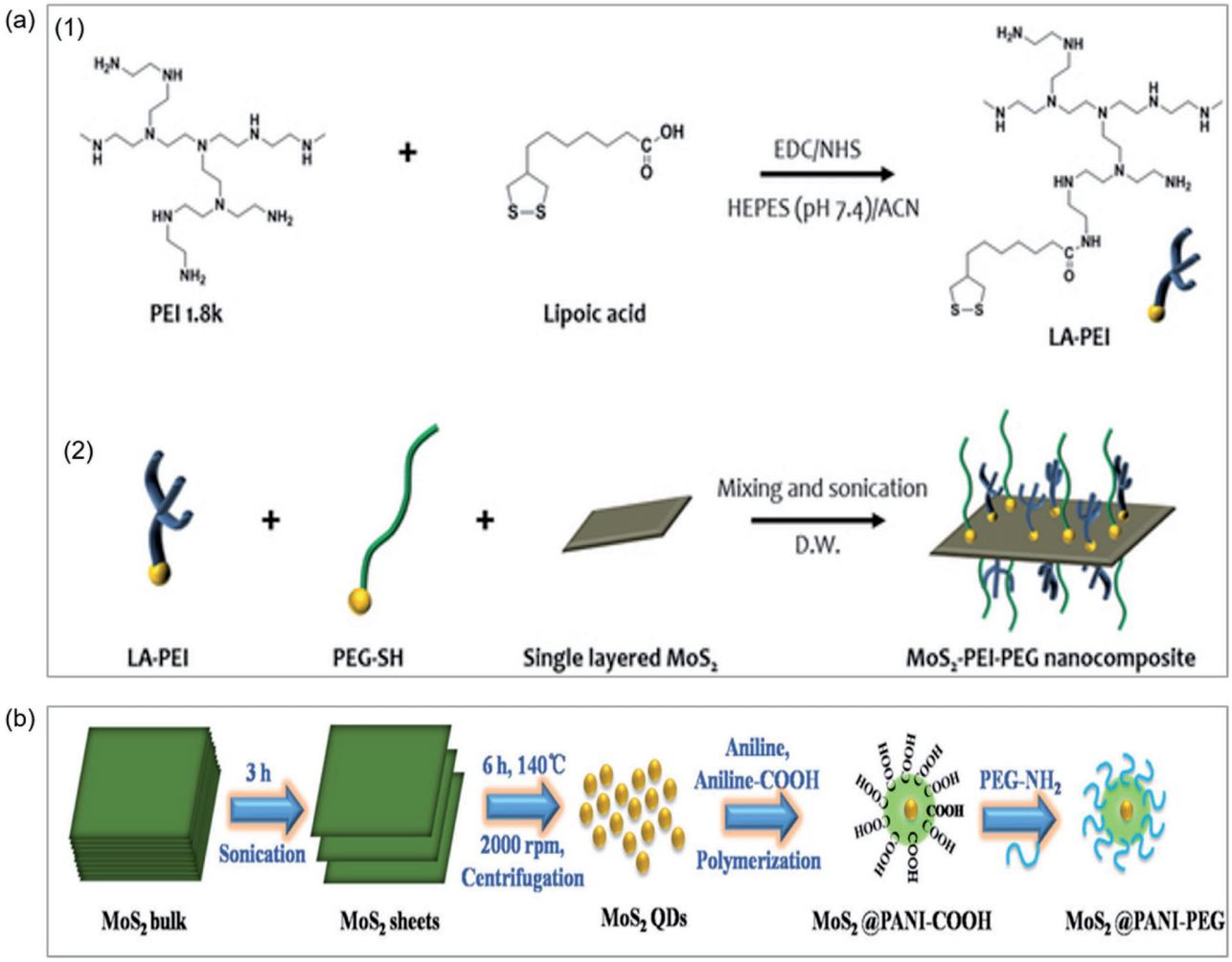

Figure 9. a) Synthetic scheme of MoS_2–polyethylenimine–poly(ethylene glycol) (MoS_2–PEI–PEG) nanocomposite: (1) synthesis of lipoic acid (LA)–PEI through equivalent 1-ethyl-3-(3-(dimethylamino) propyl) carbodiimide hydrochloride/*N*-hydroxysuccinimide (EDC/NHS) amide coupling reaction; (2) modification of the MoS_2 surface with LA–PEI and thiolated PEG (PEG–SH) by disulfide-bond formation. HEPES = 4-(2-hydroxyethyl)-1 piperazineethanesulfonic acid, ACN =acetonitrile, D.W. = distilled water. Reproduced with permission.[131] Copyright 2015, Wiley-VCH. b) Diagram of the synthesis process for MoS_2@polyaniline (PANI) nanohybrids. Reproduced with permission.[130] Copyright 2016, American Chemical Society.

chitosan, a naturally occurring linear cation polysaccharide, through electrostatic attraction during the exfoliation process.[25] The functionalized biocompatible chitosan–MoS_2 nanosheets were further loaded with doxorubicin (DOX), which could be controllably released upon the photothermal effect induced by NIR laser irradiation to realize the combination of chemotherapy and PTT for cancer treatment. Additionally, Shi and co-workers reported another drug-delivery implant for efficient NIR-triggered synergistic tumor hyperthermia, by homogenizing the hydrophobic polymer poly(lactic-*co*-glycolic acid) (PLGA) with MoS_2 in NMP solution to form a multifunctional oleosol.[57] As a result, the PLGA-containing implant was proved to have multiple stimuli-responsive drug release, high in vivo hemo-/histocompatibility, and enhanced synergistic tumor therapeutic outcome, which provide a promising clinical translation potential for efficient localized tumor therapy. In 2016, F127, a nonionic triblock copolymer, assisted synthesis, and simultaneously functionalized ultrasmall $MoSe_2$ nanodots were reported by Wang and co-workers.[112] These F127-modified $MoSe_2$ nanodots showed good colloidal stability and biocompatibility, as well as photothermal stability, which could efficiently kill HeLa cells at low concentration under NIR laser irradiation. What is more, PVP-functionalized ultrasmall MoS_2 nanoparticles, during the hydrothermal method, were demonstrated by Gu and co-workers,[148] where the as-prepared PVP–MoS_2 was proved to be able to detect H_2O_2 as well as serum glucose level, showing potential to be used as a medical diagnosis tool.

4.2. Biological Molecules

Biomolecules such as proteins, peptides, or nucleic acids are also widely used in the functionalization of TMDCs, as they are intrinsically biocompatible and can enable TMDCs to display the properties and functions that are similar to normal biomolecules

present in cellular systems.[149] Similar to polymers, biomolecules can also be modified to TMDCs chemically or physically.

Proteins are biological molecules formed by amino acid residues, and typically contain both hydrophilic and hydrophobic segments,[150] making it potentially possible for them to functionalize TMDCs as amphiphilic modifiers through physical absorption. BSA has been reported to function as a simultaneous stabilizer and a functional agent during the TMDC synthesis process to produce different water-dispersible TMDC nanostructures with good biocompatibility.[44,69,123] As an interesting paradigm, Yong et al. developed BSA-coated WS_2 flakes as drug carriers to load a significant amount of photosensitizer, methylene blue, for combined photothermal and photodynamic treatment of cancer cells.[44] Thus, by modifying TMDCs with suitable functional materials, one can not only enhance the compatibility and stability of TMDCs in physiological systems, but also exploit the unique properties of TMDCs as a direct source for synergistic therapy. In addition to BSA, other protein-related materials, such as hemin molecules[133] or regenerated silk fibroin (RSF),[151,152] have also been reported to enable TMDCs with high dispersion in aqueous solutions. For instance, Chen and co-workers reported silk-protein-coated MoS_2 flakes simply by adding MoS_2 dispersion into an RSF aqueous solution.[152] The as-prepared RSF/MoS_2 hybrids further demonstrated less cytotoxicity than pristine MoS_2, as well as high photothermal capability on ablating HeLa cells, and it is expected that they can be used as a photothermal agent in future cancer treatment.

Peptides are also formed by the assembly of amino acid residues, but with much shorter sequences than proteins. Their modification on TMDCs is mostly realized through either thiol chemistry or chemisorption.[109,153,154] For example, GSH was reported to functionalize MoS_2 nanodots through thiol chemistry.[109] It is proved that GSH is the most appropriate molecule for modification of MoS_2 nanodots to realize an ultrasmall hydrodynamic size and high stability in physiological solutions, compared with other thiol-containing molecules, such as PEG and cysteine. In addition, a multifunctional nanosystem based on LA-PEG–MoS_2 with a pH-responsive charge-convertible peptide (LA-K11(DMA)) modification was reported by Peng et al.[154] With this charge-convertible peptide, a positively charged photosensitizer, toluidine blue O (TBO), could be easily loaded or released on/from the MoS_2 under different pH conditions. As was illustrated, under acidic conditions in the tumor areas, the binding force between positively charged TBO and MoS_2 could be reduced when the negatively charged LA-K11(DMA) peptide was converted into a positively charged one, resulting in TBO release with recovered fluorescence and photoinduced generation of reactive oxygen species (ROS), as well as photoinduced hyperthermia of MoS_2. Under normal conditions, such fluorescence and ROS generation of TBO were significantly decreased by MoS_2, as TBO is strongly absorbed on negatively charged LA-K11(DMA) peptide. In this way, the as-prepared multifunctional nanosystem could realize a highly specific and efficient synergistic antitumor effect with photoinduced hydrothermal therapy and ROS generation.

Small organic molecules such as amino acids or nucleic acids are also used to modify TMDCs for biomedical application. Due to their small physical size, it is easier for small organic molecules to realize cellular uptake when compared with polymers or other big biomolecules. In 2014, Jeng and co-workers reported a concurrent liquid-phase exfoliation and functionalization of MoS_2 using thioglycolic acid (TGA) as an efficient bifunctional ligand.[127] In a typical experiment, TGA could not only exfoliate bulk MoS_2 and modify the surface of MoS_2 via thiol chemistry with carboxylic acid end groups to improve the dispersion of the MoS_2 monolayer in water, but could also subsequently synthesize water-soluble MoS_2 QDs with sustained fluorescence emission, which could be utilized as cell biomarkers and in some other biomedical applications. In 2017, an amino-acid-induced solution-processed simultaneous exfoliation and in situ covalent functionalization of MoS_2 were proposed by Satheeshkumar et al.[84] who found that the N-terminal binding (NH_2) of amino acids is much more favorable than the C-terminal binding (carboxylic acid) to the sulfur defects on exfoliated MoS_2. The functionalized MoS_2 flakes through this simple nontoxic method exhibited excellent biocompatibility, and it can be envisioned that other MX_2 compounds of TMDCs may be also exfoliated and functionalized by this method.

Additionally, nucleic acids such as DNA play an important role in functionalizing TMDCs for biomedical applications.[155,156] For example, Leong and co-workers designed a drug-delivery system that used DNA oligonucleotides with thiol-terminated groups to functionalize MoS_2 nanosheets by binding to sulfur-atom defect vacancies on the MoS_2 surfaces (**Figure 10**).[156] DNA-based aptamers were further introduced to the system as linkers to stimulate the layer-by-layer self-assembly of the MoS_2 NS due to the complementary hybridization of DNA–oligonucleotide pairs, and thus to form a Testudo-like multilayered MoS_2 NS. This as-prepared Testudo-like MoS_2 superstructures could stay very inert and resistant to the damaging intracellular DNA enzymes because of the "shield" function of the MoS_2 NS. Nevertheless, in cancer cells, where ATP molecules are of high concentration, these multilayered superstructures could autonomously disassemble as a consequence of stronger binding of ATP molecules with the linking aptamers. Consequently, with the combined effects of DNA specificity and the 2D plane of the MoS_2, this newly synthesized nanosystem could realize a targeted stimuli-responsive drug delivery in cancer cells.

4.3. Silica

Inorganic materials such as silica provide an alternative to organic modifiers in the functionalization of TMDC nanostructures for bioapplications. Mesoporous silica provides an easy platform to accommodate various guest molecules, such as drugs, into their pores,[157] and thus are widely used in the functionalization of TMDCs.[33,43,158] Recently, Lee et al. reported a silica-coating functionalization, which provides biocompatibility to hydrophobic single-layered MoS_2.[43] As shown in **Figure 11**, a silica layer was first formed on the surface of chemically exfoliated MoS_2 by sol–gel condensation of a silica precursor with CTAB in aqueous conditions. Later, amine groups were introduced for further PEGylation and DOX loading. The results showed that this colloidal

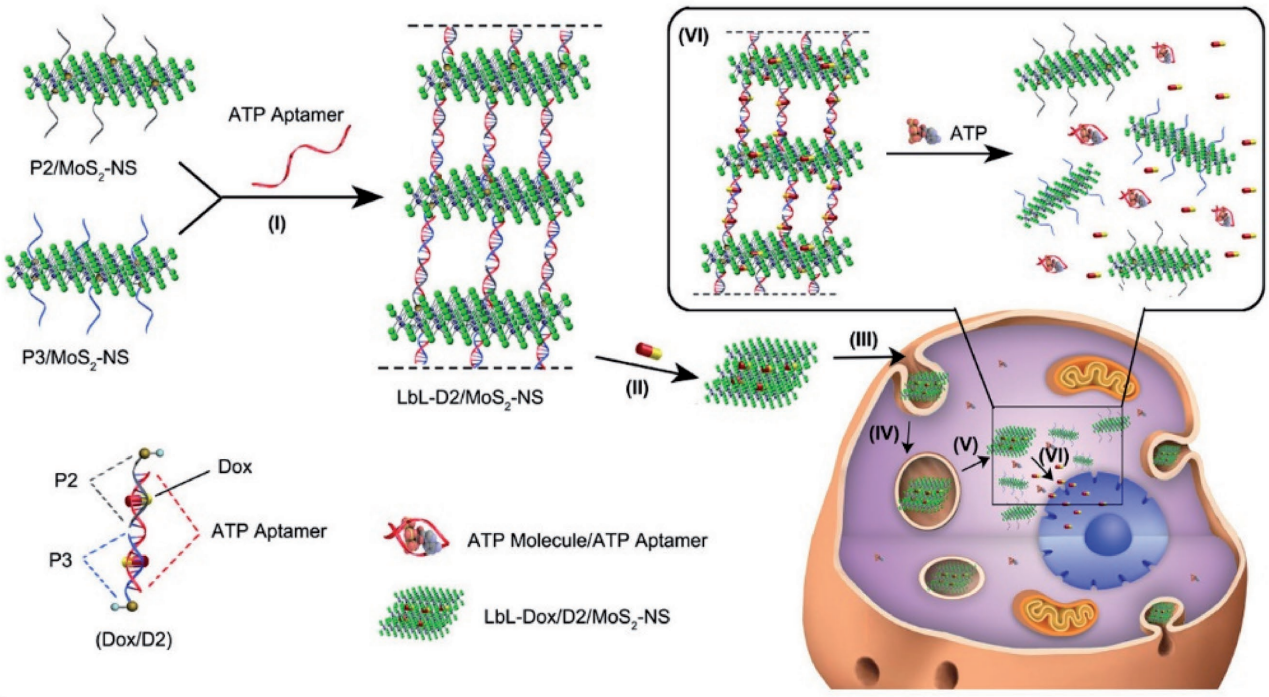

Figure 10. Schematic illustration of the formation of multilayered doxorubicin/two kinds of thiolated ssDNA (P2 and P3)/MoS_2 nanosheets (DOX/D2/MoS_2 NS) and their intracellular DOX-release process: (I) ATP-aptamer-induced layer-by-layer assembly; (II) DOX loading in multilayered nanostructures; (III) in vitro treatment of DOX/D2/MoS_2 NS; (IV) cell uptake through endocytosis; (V) endosomal/lysosomal escape; (VI) ATP-induced DOX release in the cytosol. LBL = layer-by-layer. Adapted with permission.[156] Copyright 2017, American Chemical Society.

stable single-layered MoS_2 covered with porous silica and PEG might have an application in the field of photothermally responsive drug-delivery systems. Alternatively, Su et al. demonstrated the synthesis of sandwich-like biocompatible MoS_2/mesoporous organosilica (MoS_2/MOS) nanosheets assisted by CTAB during the modification process.[158] These MoS_2/MOS nanosheets possessed an array of ordered mesopores, high surface area, and large pore volume, exhibiting high photothermal conversion ability and controllable drug-release properties for cancer treatment.

5. Conclusion

TMDCs are emerging candidates in nano-biomedicine. Their distinctive structures and chemical/physical properties endow

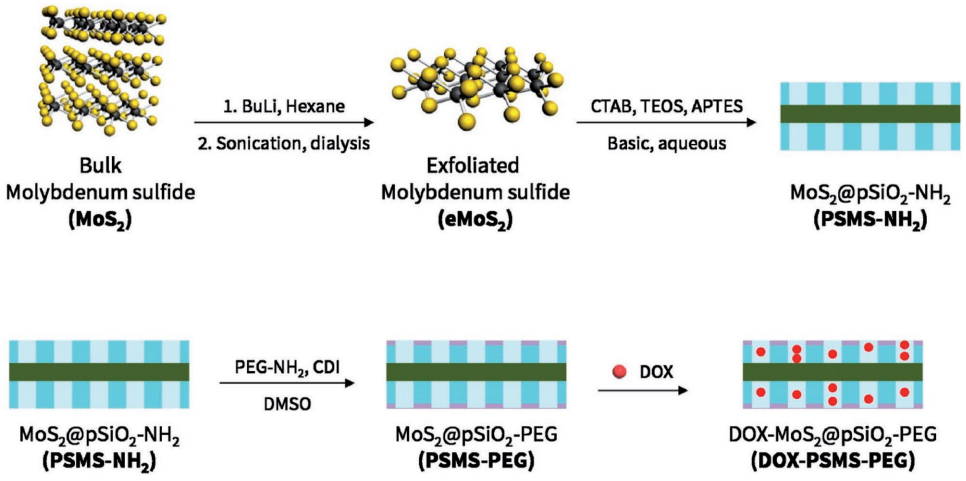

Figure 11. Synthesis of silica-modified MoS_2 (PSMS–NH_2) as well as its PEGylation and DOX loading. TEOS = tetraethyl orthosilicate, APTES = 3-aminopropyl)triethoxysilane. Adapted with permission.[43] Copyright 2016, American Chemical Society.

them with extensive applications in multimodal imaging, as well as in synergistic therapy for cancer treatment. Before TMDCs are used practically for theranostic applications, they should be tested for their physiological dispersibility and stability, biocompatibility, and biodistribution, as well as targeting or other biomedical capabilities.[159,160] Over the last few decades, studies of the synthesis and surface modification of TMDC-based nanomaterials have been extensively carried out, and significant progress has been attained, enabling these materials for more efficient theranostic applications in the biological environment. Here, we have summarized the basic design principles, solution-based synthesis strategies, as well as commonly used surface modification routes for TMDC-based nanomaterials for biomedical applications. Generally, in order to apply TMDCs in biological systems, they must meet several requirements, such as water solubility, good physiological dispersibility and stability, biocompatibility, and low toxicity, as well as a relatively small or ultrasmall size. To this end, solution-based synthesis methods including both bottom-up and top-down methods are mostly used to obtain water-soluble TMDC nanomaterials. Surface functionalization of TMDCs via chemical and physical routes also provides possibilities of tailoring the diverse properties of TMDCs for biomedical use. We have shown that through appropriate synthesis and modification routes, TMDCs can be molded to have improved water solubility and biocompatibility, as well as to realize a wide range of biomedical applications such as multimodal bioimaging, drug delivery, synergistic therapy, and biosensors.

However, although the advances are exciting and encouraging, there are still numerous limits among the current synthesis and functionalization methods. First, the size, shape, morphology, and thickness of TMDCs usually affect their effective performance, such as their penetration ability or therapeutic effects.[25,34,161] Nevertheless, most TMDC layers synthesized by liquid exfoliation possess inconsistency in thickness, and the lateral sizes of TMDCs resulting from chemical or electrochemical intercalation methods are usually not easy to control.[162] In addition, controlled and desirable structural parameters can be synthesized by wet-chemical synthesis strategies, but their strict reaction conditions, such as high temperature/pressure and inert gas atmosphere, still greatly limit their practical application. Therefore, establishing standardized green and easy-to-perform strategies to synthesize precisely controlled uniform TMDCs still remains a challenge for better biomedical application. Second, suitable and nontoxic functionalization of TMDCs plays an important role in controlling their biocompatibility, biodistribution, and toxicity, as well as theranostic performance in practical applications. However, functional groups modifying TMDCs through thiol chemistry or physical absorption are not strong enough because they can be easily influenced by varied pH, temperature or the presence of GSH, and thus exhibit instability in complicated physiological environments, which call for alternative strategies to efficiently modify TMDCs without being easily affected by the complicated biological surroundings. Moreover, considering the multiple and rigid steps of synthesis and functionalization, it is also of urgency to find effective strategies to prepare and modify mass TMDCs simultaneously into biocompatible materials for biomedical applications in a practical way. Finally, as TMDCs are applied for biomedical applications, biosafety is another crucial factor for nanomaterials in biological use. Once the biomedical theranostic applications of TMDCs are achieved, these materials should be thoroughly eliminated from biological systems without causing any harmful effects. This is of great importance before translating such theranostic materials to clinical application. In this aspect, it is very important and useful to look into the biosafety aspect of TMDC-based nanomaterials, which may offer further guidance for better TMDC synthesis and functionalization. Therefore, future work may also pay attention to the comprehensive biosafety evaluation for the synthesis of biofriendly TMDCs in biomedical applications.

In conclusion, despite some challenges regarding the synthesis and functionalization methods that need to be overcome, TMDC-based nanomaterials are still considered as a promising tool for various biomedical applications. In addition to TMDCs, other 2D nanomaterials, such as black phosphorus, have also been gaining more and more attention during the last decade. As a 2D nanomaterial, black phosphorus also exhibits a large surface area for massive functionalization loading.[163] Besides, it also possesses large NIR extinction coefficient, high photothermal conversion efficiency, and low cytotoxicity, and can be used in PTT cancer treatment.[164,165] Such 2D nanomaterials have been reported to have good biocompatibility by liquid exfoliation.[166] Likewise, the synthesis and functionalization methods mentioned above may also be applied to other 2D nanomaterials for biomedical use. Hence, extensive research efforts are still needed to develop safer and more efficient synthesis and modification methods to fully utilize the distinctive advantageous properties of TMDCs in the biomedical field. It is expected that TMDCs will offer a promising clinical translation potential for efficient biomedical applications.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomedical applications, functionalization, nanomaterial design, synthesis, transition-metal dichalcogenides

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