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Recent development and prospects of surface modification and biomedical applications of MXenes

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MXenes, as a novel kind of two-dimensional (2D) materials, were first discovered by Gogotsi *et al.* in 2011. Owing to their multifarious chemical compositions and outstanding physicochemical properties, the novel types of 2D materials have attracted intensive research interest for potential applications in various fields such as energy storage and conversion, environmental remediation, catalysis, and biomedicine. Although many achievements have been made in recent years, there still remains a lack of reviews to summarize these recent advances of MXenes, especially in biomedical fields. Understanding the current status of surface modification, biomedical applications and toxicity of MXenes and related materials will give some inspiration to the development of novel methods for the preparation of multifunctional MXene-based materials and promote the practical biomedical applications of MXenes and related materials. In this review, we present the recent developments in the surface modification of MXenes and the biomedical applications of MXene-based materials. In the first section, some typical surface modification strategies were introduced and the related issues were also discussed. Then, the potential biomedical applications (such as biosensor, biological imaging, photothermal therapy, drug delivery, therapeutic nanoplatforms, and antibacterial agents) of MXenes and related materials were summarized and highlighted in the following sections. In the last section, the toxicity and biocompatibility of MXenes *in vitro* were mentioned. Finally, the development, future directions and challenges about the surface modification of MXene-based materials for biomedical applications were discussed. We believe that this review article will attract great interest from the scientists in materials, chemistry, biomedicine and related fields and promote the development of MXenes and related materials for biomedical applications.

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1. Introduction

Nanomaterials have at least one dimension in the nanometer scale, and they have gradually become the research focus of numerous researchers with the rapid development of nanoscience and nanotechnology.^{1,2} Thereinto, if only one dimension is restricted, the materials can be called two-dimensional (2D) nanomaterials.^{3,4} Meanwhile, various 2D nanomaterials have been put forward such as graphene, molybdenum disulfide, and black phosphorus nanosheets.^{5–7} Due to

the unique 2D structure, most 2D nanomaterials possess excellent physical and chemical properties, which make them suitable for diverse applications, including energy, environment, and biomedicine.^{8–13} Recently, MXenes, as a fire-new kind of 2D nanomaterials, have attracted increasing interest for different applications since 2011.¹⁴ Being different from other 2D nanomaterials, MXenes usually consist of transition metal carbides, nitrides, and carbonitrides.^{15,16} These materials can be generally expressed by a simple formula $M_{n+1}X_n$ ($n = 1-3$), where M is an early transition metal (Ti, Zr, Cr, V, Hf, Nb, Sc, Ta, Mo), and X is a carbon or nitrogen.¹⁷ Up to now, more than seventy MXenes with different compositions have been theoretically predicted.¹⁸ Nevertheless, only about twenty MXenes with different compositions can be obtained *via* experimental methods.¹⁹ Therefore, more MXene-based materials are expected to be prepared experimentally and join the family of 2D nanomaterials in future.

Recently, MXenes have attracted a great deal of research interest in biomedical applications.^{14,20} As a novel type of 2D

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nanomaterials, MXenes have inherited multitudinous advantages of common 2D materials, including large specific surface areas and outstanding electronic, mechanical, and physicochemical properties.²⁰ In addition to these advantages, MXene-based materials possess another two attractive properties, which can provide a guarantee for biomedical applications.²¹ On the one hand, there exist a number of functional groups (*e.g.*, hydroxyl, fluorine, and oxygen) on their surface. They can be utilized to load various drugs, hydrophilic biomacromolecules, and functional nanoparticles for complicated surface modification before further biomedical applications.^{22–25} For instance, Xie *et al.* converted the hydroxyl groups on the surface of MXenes to oxygen-containing composites and utilized these functionalized MXenes to adsorb metal ions.²⁶ On the other hand, the remarkable biocompatibility of MXene-based materials has been extensively demonstrated by some reports.²⁷ It is worth mentioning that Ke *et al.* demonstrated the excellent cytocompatibility of several common MAX phases (the raw materials of most MXene-based materials).²⁸ Hence, MXene-based materials should be expected to possess a high potential for various biomedical applications.

With the rapid development of MXene-based materials, various preparation methods of MXene-based materials have been developed in succession.²⁸ It can be divided into two main strategies: top-down approaches and bottom-up methods. Both methods can realize the successful preparation of single-layer, few-layer, and multilayer nanostructures of MXenes. Nevertheless, most MXene-based materials obtained

through traditional preparation methods possess overlateral size of sheets, which limits their further biomedical applications.^{29,30} Fortunately, Lin *et al.* develop a new preparation method of typical MXenes (Ti_3C_2 and Nb_2C), which possess nanoscale-lateral sizes (about 100 nm) and single-atomic thickness (about 1 nm).^{31,32} Furthermore, raw MXenes are prone to aggregate and precipitate in physiological medium, and display poor water dispersibility. Especially in biomedical applications, poor water dispersibility would impede their effective transport within the blood circulation system and internalization by cells. More importantly, MXene-based materials might accumulate in reticuloendothelial systems (RES) after intravenous administration, which would result in potential toxicity through long-term accumulation.³³ To overcome these problems, various hydrophilic polymers have been decorated on the surface of MXenes through non-covalent interaction or physical adsorption.³⁴ However, non-covalent interactions and physical adsorption cannot maintain enough fastness in some practical applications.^{35,36} More importantly, common conjugating drugs through physical adsorption cannot realize controlled release in the true sense. Therefore, it is still urgently required to develop covalent methods and dynamic approaches of surface modification for biomedical applications of MXene-based materials.

In this mini-review, we summarize and discuss the very recent advances of MXene-based materials in biomedical applications. Firstly, we highlight several common surface modification strategies of MXene-based materials, which can be mainly divided into covalent and non-covalent methods.



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Besides, various biomedical applications of MXene-based materials are further discussed and prospected, including bio-sensing, bioimaging, photothermal therapy, drug therapy, and theranostic and antimicrobial agents. Furthermore, we discuss the toxicity and biocompatibility of MXene-based materials. At the end of this mini-review, current challenges and future prospects of MXene-based materials in biomedical applications have also been discussed.

2. Surface modification and functionalization strategies of MXenes

MXenes, as a novel kind of 2D nanomaterials, possess numerous merits, such as large specific surface area, great biocompatibility, rich surface functional groups, outstanding electronic, mechanical, and physicochemical properties.³⁷ Nevertheless, even with in-depth research on MXene-based materials, these excellent properties still cannot meet the requirements for various applications.³⁸ Therefore, surface modification and functionalization is necessary for improving their properties and endowing new functions. Fortunately, there exist a great number of functional groups on the surface of MXene-based materials, which can be utilized to modify the surface of MXene-based materials through covalent methods.³⁹ Furthermore, due to the unique 2D structure, several studies reported surface functionalization of MXene-based materials *via* non-covalent interactions and physical adsorption.⁴⁰ In this part, we introduce some typical surface modification strategies of MXene-based materials and corresponding application prospects.

Self-initiated photo-grafting and photopolymerization (SIPGP) is a facile and simple polymerization method.^{41,42} Compared with common polymerization methods, high-efficiency SIPGP no longer requires anchoring layers, self-

assembled monolayers (SAMs), and initiators.⁴² It only needs direct brush grafting on the surface of materials in a one-step reaction at room temperature under UV-irradiation.⁴³ More importantly, SIPGP has been successfully applied on a wide range of substrates including graphene, carbon nanotube, silicon-based substrate, and diamond.^{44–47} Recently, Chen and co-workers have reported a robust strategy, which is grafting poly(2-(dimethylamino)ethylmethacrylate) (PDMAEMA) brushes on the surface of MXenes through SIPGP.⁴⁸ As shown in Fig. 1A, V₂C MXenes were prepared by soaking V₂AlC powders in hydrofluoric acid at room temperature. Then, they utilized the hydroxyl groups on the surface as the photo-active sites to allow further growth and amplification of the polymer brushes *via* SIPGP. Finally, the V₂C@PDMAEMA hybrid materials were further explored for their CO₂ and temperature dual-responsive properties. To the best of our knowledge, this study is the first and single report about modifying MXene-based materials through surface-initiated polymerization. It is hoped that more surface modification strategies of MXene-based on controlled polymerization will be developed for biomedical applications.^{49–57}

Aryl diazonium chemistry has attracted significant research interest due to its extensive application prospects.⁵⁸ Especially in surface chemistry, it is well known that aryl diazonium can form covalent bonds at the surface of diverse substrates, including carbon materials, semiconductor, metal oxides, and metal nanoparticles.^{59,60} Subsequently, Zhang and Wang *et al.* found that aryl diazonium salts can be covalently attached onto the MXene surface in the form of stable Ti–O–C bonds. It is worth mentioning that the introduction of aryl diazonium salts would lead to an increase in the interlayer spacing of MXene-based materials.⁶¹ As displayed in Fig. 1B, the prepared MXenes were firstly intercalated by Na⁺ ion. Then, phenylsulfonic groups could be immobilized directly on the surface of the MXenes *via* aryl diazonium chemistry. On account of diazonium ions' intercalation and electroactive groups grafting, the



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medical applications of two-dimensional materials and their composites, energy materials and devices, and computational material science.

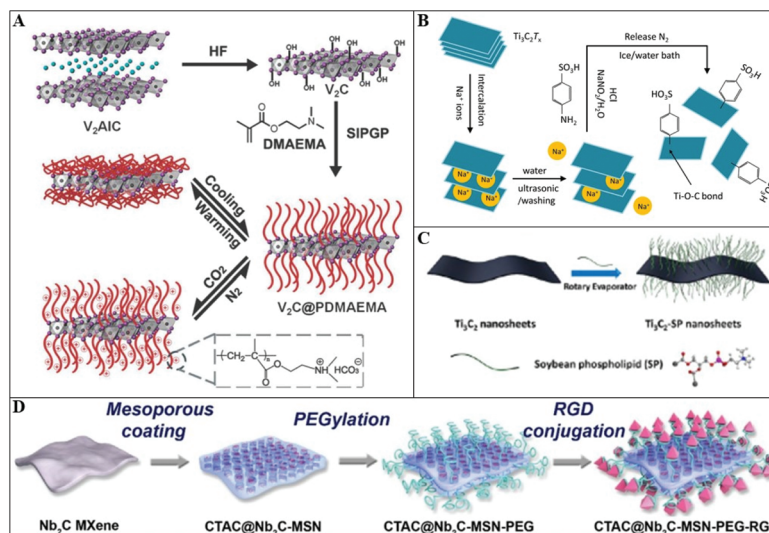
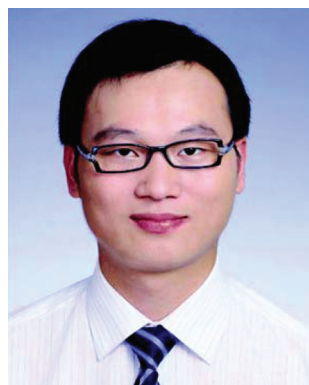


Fig. 1 Several surface modification methods of MXene-based materials: (A) SIPGP polymerization. Reprinted with permission.⁴⁸ Copyright 2014, The Royal Society of Chemistry. (B) Aryl diazonium chemistry. Reprinted with permission.⁶¹ Copyright 2018, Elsevier. (C) Physical adsorption. Reprinted with permission.³² Copyright 2017, American Chemical Society. (D) Covalent method through APTES. Reprinted with permission.⁶⁵ Copyright 2018, Ivyspring International Publisher.

chemically functionalized MXenes possesses an enhanced supercapacitive performance. However, the surface modification of MXene-based materials through aryl diazonium chemistry is still at the primary stage. It is promising for conjugating various functional groups and molecules onto the surface of MXene-based materials through aryl diazonium chemistry.

It can be known from the aforementioned discussion that MXenes possess numerous excellent properties for biomedical applications. Nevertheless, non-functionalized MXenes possess poor water dispersibility and it is difficult to form a stable suspension with them in physiological solution, which

would severely limit their biomedical applications.⁶² For conquering this obstacle, diverse hydrophilic polymers are applied for surface modifications of MXene-based materials. For example, soybean phospholipid (SP), as the natural polymer, has been immobilized on the surface of MXenes through physical adsorption, which is shown in Fig. 1C.³² After modification of SP, MXene-based composites were verified to possess enhanced permeability, stable circulation, and retention ability.⁶³ Furthermore, PEGylation of MXenes has also been demonstrated to be an economical and efficient modification molecule for improving the water dispersibility of MXenes *via* electrostatic adsorption.³⁴ Moreover, Chen and Lin *et al.* utilize



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the non-covalent interactions to modify poly(vinylpyrrolidone) (PVP) onto the surface of MXene-based materials.⁶⁴ Meanwhile, there also emerged another potential problem that non-covalent and physical adsorption interactions are not stable enough for some biomedical applications. Fortunately, very recently, Han *et al.* developed a covalent strategy to conjugate PEG on the surface of MXenes for biomedical applications (Fig. 1D).⁶⁵ They used (3-aminopropyl)triethoxysilane (APTES) as a bridge to link MXenes with PEG. On the one hand, APTES could bond with hydroxyl and make MXenes bond with amino groups. On the other hand, the amino groups could react with PEG to form PEGylated MXenes. In addition, MXene-based materials possess unusual 2D structure and large specific surface area, which is well suited for drug loading in biomedical applications.⁶⁶ Hence, many researches have examined drug loading on the surface of MXene-based materials and utilized MXenes as substrates of drug delivery applications.⁶⁷ However, most modification strategies of drug loading are also through non-covalent and physical adsorption interactions, which also cannot maintain enough fastness in practical biomedical applications.^{66,68} More importantly, most anti-cancer drugs are likely to harm normal cells and the therapeutic efficiency is dependent on the concentration of effective drugs in the cancers.^{69,70} Thus, controlled drug release is crucial for the construction of MXene-based drug delivery systems.⁷¹ However, common non-covalent and physical adsorption strategies cannot realize controlled release. As a consequence, other surface modification strategies through covalent and dynamic approaches are expected to be developed for conjugating polymers or other functional components on MXenes to realize better performance for drug delivery applications. After surface modification and functionalization, MXene-based materials would possess a great number of outstanding properties and have also shown great potential for multitudinous applications including biomedicine, energy, and environment.^{72–88} Among these, the biomedical applications of MXene-based materials for biosensing, bioimaging, photothermal therapy, drug delivery system, theranostic nano-platforms, and antibacterial agents have been summarized in the following sections.

3. Biomedical applications

3.1. Biosensing

Biosensing, as a useful tool for analyzing targeted biomolecules, has received tremendous attention in various applications.^{89–92} To fabricate mediator-free electrochemical biosensors, the research on direct electron transfer (DET) between an enzyme and an electrode is of great significance.^{93,94} Nevertheless, the electroactive center of proteins is deeply buried in their protein structure and the proteins of the electrode surface generally lose their bioactivity, thus limiting DET between the enzymes and electrodes.^{95,96} To overcome this obstacle, numerous nanomaterials have been used for the immobilization of enzymes onto the electrode

surface.^{97,98} Thereinto, MXene-based materials have served as promising nanomaterials for biosensing due to their large specific surface area, outstanding electrical properties, and excellent biocompatibility.⁹⁹ For instance, Wang and Zhu *et al.* have developed a novel organ-like MXene-based nanomaterial for the fabrication of mediator-free biosensors, which displayed a low detection limit of 20 nM and a linear range of 0.1–260 μM for H_2O_2 .¹⁰⁰ As displayed in Fig. 2A, hemoglobin (Hb) was used as a model protein to be modified onto the surface of Ti_3C_2 MXene-based materials, which have an effective collision with the substrate. Fig. 2B shows the typical cyclic voltammograms (CVs) of different modified electrodes in physiological conditions (pH 7.0, 0.1 M PBS) with a scan rate of 0.1 V s^{-1} . No redox peak is observed at the Nafion/MXenes/a glassy carbon (GC) electrode (curve a), suggesting their electro-inactive state in the potential window. Furthermore, the Nafion/Hb/MXenes/GC electrode (curve b) exhibits a couple of stable and well-defined redox peaks at -0.367 V and -0.327 V vs. Ag/AgCl, demonstrating that MXene-based materials can provide a favorable microenvironment for Hb to undergo a facile electron-transfer reaction. Compared with that of curve b, the redox peaks of the Nafion/Hb/GC electrode (curve c) are 79.7% smaller, which could be ascribed to unachievable DET process between the enzyme and the electrode. All these results confirm that direct electron transfer between Hb molecules and GC electrode is greatly enhanced at the Nafion/Hb/MXene/GC electrode. Fig. 2C and D are the amperometric responses of the Nafion/Hb/MXenes/GC electrode at -0.35 V with the addition of different concen-

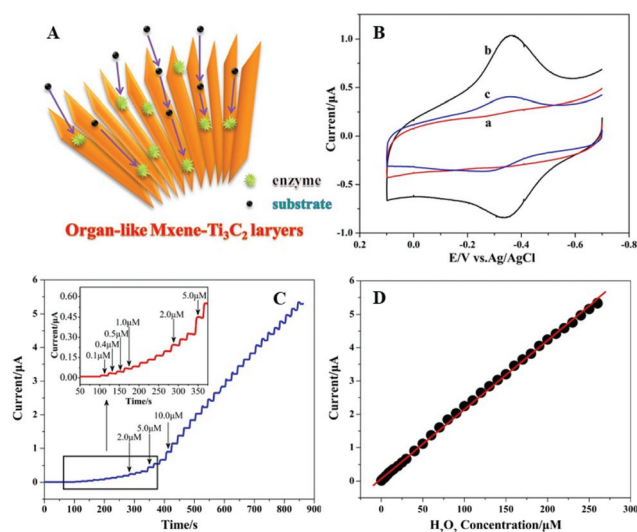


Fig. 2 The biosensor based on MXenes for the detection of H_2O_2 . (A) The schematic illustration of the organ-like structure of MXene- Ti_3C_2 encapsulating hemoglobin. (B) Cyclic voltammograms of the Nafion/ Ti_3C_2 /GC electrode (a), Nafion/Hb/ Ti_3C_2 /GC electrode (b), Nafion/Hb/GC electrode (c) in 0.1 M pH 7.0 PBS with a scan rate of 0.1 V s^{-1} . (C) Typical current-time response of the Nafion/Hb/ Ti_3C_2 /GC electrode at -0.35 V for successive addition of H_2O_2 in stirred 0.1 M pH 7.0 PBS. (D) The steady state current vs. H_2O_2 concentration. Reprinted with permission.¹⁰⁰ Copyright 2015, The Electrochemical Society.

trations of H_2O_2 in PBS solution (pH 7.0). The biosensors exhibited good performance for the detection of H_2O_2 with a wide linear range of 0.1–260 μM for H_2O_2 , as well as an extremely low detection limit of 20 nM for H_2O_2 . In addition, the amperometric glucose biosensor and nitrite biosensor based on MXene-based materials have also been reported.^{101,102} On the one hand, MXene-based materials possess great conductivity and other electrical properties. On the other hand, due to the unique 2D structure, the MXene-based materials possess a large specific surface area available for enzyme binding. Therefore, MXene-based materials are suitable for enzyme conjugation and exhibit great potential for biosensing applications.

3.2. Bioimaging

As mentioned above, MXene-based materials possess a rosy prospect in biosensing applications. Meanwhile, fluorescent nanomaterials can also play a pivotal role in biosensors for marking targeted biomolecules.¹⁰³ However, no photoluminescence response could be detected in the conventional MXene-based materials, thus limiting their further biomedical applications. Especially in bioimaging, it has attracted multitudinous luminescent nanomaterials to be applied. Among various luminescent nanomaterials, QDs derived from 2D materials have gradually become the most promising alternative candidates for bioimaging. Thereinto, graphene QDs, boron nitride QDs, and molybdenum disulfide QDs have got extensive reports.^{104–106} Hence, it is urgently required to develop novel luminescent nanomaterials based on MXenes. Fortunately, Xue and co-workers reported the preparation of water-soluble Ti_3C_2 MXene QDs (MQDs) through a facile hydrothermal method and explored their potential bioimaging application.¹⁰⁷ As seen in Fig. 3A, the MQDs were prepared through a one-step hydrothermal method by fragmentating monolayer Ti_3C_2 MXene nanosheets, which could be attributed to the edge effects and quantum confinement. Through the adjustment of reaction temperature, the average size of MQDs can be tailored. Fig. 3B is the TEM image of MQD-100. It is obvious that MQD-100 are monodisperse and possess a uniform lateral particle size of about 1–5 nm. Due to the uniform nanoscale size, intensive luminescence, and excellent biocompatibility, MQD-100 could easily penetrate into the cells through endocytosis and were utilized for biological imaging (Fig. 3C). Similarly, Zhou *et al.* developed a facile synthetic method of amphiphilic MXene quantum dots using solvothermal treatment of $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes in dimethylformamide (DMF) for only 2 h and investigated their ability for cell imaging.¹⁰⁸ Furthermore, Wang and Geng *et al.* demonstrated a novel fabrication method for the preparation of luminescent nanomaterials based on ultrasmall (Ti_3C_2) MXene sheets, which employs simultaneous layer cutting and stacking cleavage with a mild reaction in aqueous tetramethylammonium hydroxide (TMAOH) instead of the hydrothermal method (Fig. 3D).¹⁰⁹ Thus, it is expected that more luminescent nanomaterials based on other MXenes can be developed for bioimaging application.

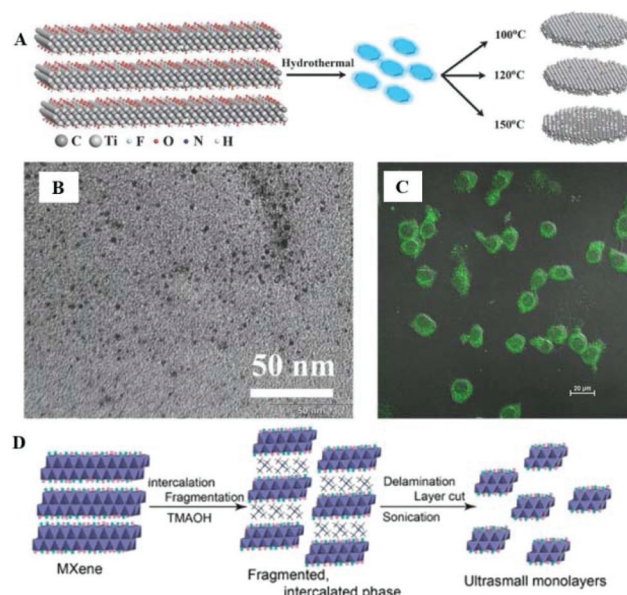


Fig. 3 (A) Schematic diagram of the preparation of MQDs. Reprinted with permission.¹⁰⁷ Copyright 2017, WILEY-VCH. (B) The TEM images of MQD-100. (C) Merged images of the bright-field and the confocal images of MQD-100 (488 nm). (D) Schematic illustration of the synthetic process for preparing luminescent Ti_3C_2 sheets. Reprinted with permission.¹⁰⁹ Copyright 2017, American Chemical Society.

Except for luminescent imaging, it has been adequately demonstrated that MXenes can also be utilized in other imaging methods, including magnetic resonance (MR) imaging, computed tomography (CT) imaging, and photoacoustic (PA) imaging.^{40,110} For example, the manganese oxide component (MnOx) can be modified onto the surface of MXene-based materials, which is conducive for further MR imaging of MXene-based materials.⁴⁰ Besides, some specific MXene-based materials (Ta_4C_3) contain specific tantalum element with high atomic number ($Z = 73$), which could make MXene-based materials desirable contrast agents for CT imaging.⁴⁰ In addition, high-efficiency photothermal conversion of MXene-based materials has been widely reported. The great photothermal-conversion performance of MXene-based materials can endow them with potential ability for PA imaging.¹¹⁰

3.3. Photothermal therapy and drug delivery system

Recently, cancer has gradually become one of the most dangerous diseases that endanger human beings. Nowadays, common therapeutic strategies of cancer mainly contain operation, chemotherapy, and radiotherapy.¹¹¹ Nevertheless, most operation treatments cannot remove all the cancerous tissues completely. Furthermore, usual chemotherapy and radiotherapy are likely to harm the normal tissue and lead to severe side effects.¹¹² To conquer these problems, high-efficiency photothermal therapy (PTT) has attracted significant attention.¹¹³ Due to poor heat resistance of the cancer cells, PTT can transform NIR light into thermal energy at the tumor sites and inhibit the growth of cancer cells.¹¹⁴ PTT can be usually

divided into first NIR bio-window (750–1000 nm) and second NIR bio-window (1000–1350 nm). Compared with the first NIR bio-window, the second NIR bio-window possesses two advantages, including larger maximum permissible exposure (MPE) and desirable penetration depth to lasers. However, there are few reports for PPT using the second NIR bio-window due to the absence of photothermal materials with strong NIR light absorption and high-efficiency photothermal conversion in the second NIR bio-window.¹¹⁵ Fortunately, MXene-based materials can exhibit strong absorption and maintain high photothermal-conversion efficiency in both the first and second NIR bio-window. For example, Lin and Chen *et al.* utilized a novel Nb₂C-based material as a photothermal agent for highly efficient *in vivo* photothermal ablation of mouse tumor xenografts at both first and second NIR bio-windows. As displayed in Fig. 4A and B, MXene nanosheets (Nb₂C) were prepared *via* etching of Nb₂AlC ceramic powder in hydrofluoric acid at room temperature.⁶⁴ Subsequently, poly(vinylpyrrolidone) (PVP) was modified onto the surface of MXene-based materials through physical adsorption to improve their water dispersibility and biocompatibility. Fig. 4C is the TEM image of the MXene-based materials, which possess nanoscale-lateral sizes (about 100 nm) and are suitable for diverse biomedical applications. Finally, Nb₂C-PVP was investigated for the ability of photothermal ablation of mouse tumor xenografts. The tumor volumes with six groups were measured every 2 days using a digital caliper (Fig. 4G). After 16 days of different treatments, the tumor regions of the mice in the control group (Fig. 4D) are still large. On the contrary, the tumor regions of the mice in the groups of Nb₂C-PVP + NIR-I (Fig. 4E) and Nb₂C-PVP + NIR-II (Fig. 4F) completely disappeared. Fig. 4H exhibits the survival curves of mice after various treatments. It is obvious that tumor-bearing mice in groups of Nb₂C-PVP +

NIR-I and Nb₂C-PVP + NIR-II recover completely and survive over 50 days. Moreover, another type of MXene-based nanosheets (Ti₃C₂) have been conjugated with soybean phospholipid and been applied in photothermal therapy for tumor-bearing mice, which also presented excellent photothermal property.³² Due to the outstanding photothermal property, MXene-based materials have gradually served as attractive alternatives to other traditional nanomaterials for photothermal therapy. On the one hand, more varieties of MXene-based materials with excellent photothermal property for biomedical applications should continue to develop. On the other hand, multitudinous surface modification methods and biomolecules could be applied in MXene-based materials to improve their physiochemical properties for further photothermal therapy applications.

In addition to photothermal therapy, chemotherapy also plays a crucial role in cancer therapy. Most chemotherapeutics can not only harm cancer cells but also have high toxicity to normal tissue and severe side effects.¹¹⁶ Therefore, it is urgently required to develop controllable and efficient drug delivery systems. MXene-based materials, as a novel kind of 2D materials, possess multitudinous merits for the construction of drug delivery systems. For example, due to a distinctive 2D structure, MXene-based materials possess large specific surface area, which can provide abundant anchoring sites for therapeutic molecules. Furthermore, the nanoscale size of MXene-based materials is conducive for their intravenous administration and efficient accumulation into tumor sites during cancer therapy. Recently, Han and Chen *et al.* reported a high-efficiency drug delivery system based on MXenes for photothermal therapy (PPT) and chemotherapy.⁶⁷ Fig. 5A and B show the scheme of the synthetic process and modification of MXene-based materials for the construction of drug delivery

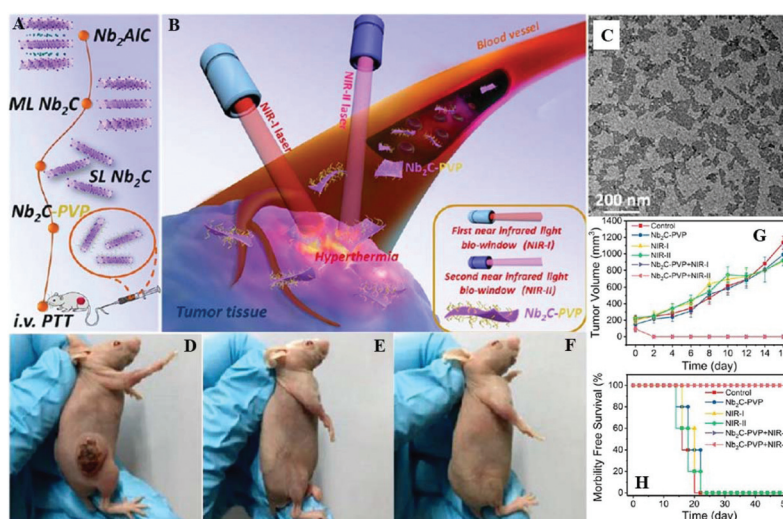


Fig. 4 (A) and (B) Schematic illustration of 2D biodegradable Nb₂C (modified with PVP) for *in vivo* photothermal tumor ablation in NIR-I and NIR-II bio-windows. (C) TEM image of Nb₂C–PVP/PBS. (D–F) Photographs of 4T1-tumor-bearing mice and their tumor regions 16 days after different treatments (control (D), Nb₂C-PVP + NIR-I (E), and Nb₂C-PVP + NIR-II (F)). (G) Time-dependent tumor growth curves (*n* = 5, mean ± SD) after different treatments. (H) Survival curves of mice after various treatments. Reprinted with permission.⁶⁴ Copyright 2017, American Chemical Society.

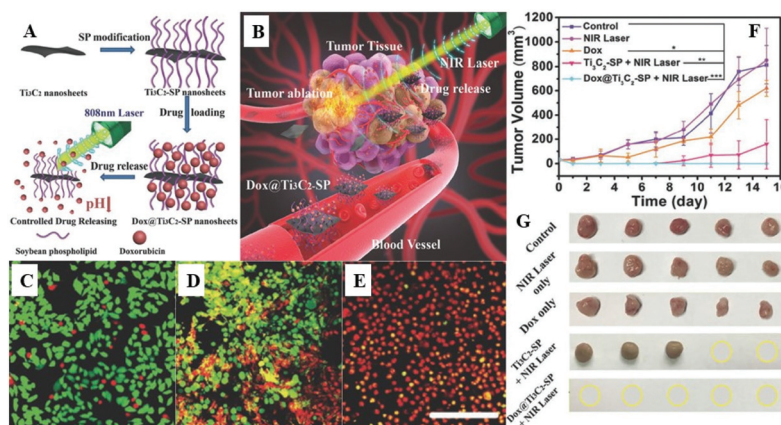


Fig. 5 (A) The scheme of surface modification of Ti_3C_2 nanosheets by SP, drug loading, and stimuli-responsive drug release through inner or external irradiation. (B) Schematic illustration of Ti_3C_2 -based drug delivery system for *in vivo* synergistic photothermal therapy and chemotherapy of cancer. (C–E) CLSM images of 4T1 cells after different treatments, including Dox@ Ti_3C_2 -SP, Ti_3C_2 -SP + laser, and Dox@ Ti_3C_2 -SP + laser. The red fluorescence represents the dead cells and green fluorescence represents the live cells. Scale bar = 50 μm . (F) Time-dependent tumor-growth curves after varied treatments. (G) Digital photo of the excised tumors from sacrificed mice in all treatment groups at the end of the therapy. Reprinted with permission.⁶⁷ Copyright 2018, WILEY-VCH.

systems. The prepared (Ti_3C_2) MXene-based materials were immobilized with soybean phospholipid (SP), which could guarantee great water dispersibility and convenient transport of MXene-based materials within the blood vessels.¹¹⁷ Subsequently, the anti-cancer drug (doxorubicin, Dox) was conjugated onto the surface of Ti_3C_2 -SP *via* electrostatic adsorption, which possesses pH-responsive and NIR-accelerated drug release. On the one hand, electrostatic interaction between Dox and Ti_3C_2 -SP could be easily interfered by H^+ , which resulted in accelerated Dox release in acidic environment. On the other hand, Dox release was significantly enhanced under irradiation state due to the local thermal effect as caused by the photothermal conversion of MXene-based materials. It is obvious that the combination of Dox@ Ti_3C_2 -SP and laser irradiation caused the most cell death, as confirmed by the almost complete red fluorescence of dead cells (Fig. 5E). On the contrary, the groups of Dox@ Ti_3C_2 -SP only (Fig. 5C) and Ti_3C_2 -SP + laser (Fig. 5D) still maintain higher cell viability. In the *in vivo* experiment, the group of Dox@ Ti_3C_2 -SP + laser exhibited the best performance, which could realize tumor eradication without reoccurrence (Fig. 5F and G). The novel drug delivery system based on MXene-based materials with pH-responsive and NIR-accelerated drug release showed high synergistic efficiency of PTT and chemotherapy. Similar to the above-mentioned works, Li and Yang *et al.* modified mesoporous-silica shell onto the surface of Ti_3C_2 to be loaded with Dox for the construction of drug delivery systems.¹¹⁸ However, to the best of our knowledge, almost all drug loading strategies of MXene-based materials is through non-covalent interactions and physical adsorption. Non-covalent interactions and physical adsorption are not sufficiently reliable in some practical applications and cannot realize controlled release to some extent. As a consequence, more drug loading and release strategies through covalent methods and formation of dynamic bonds are

expected to be developed for the construction of controlled drug delivery systems.

3.4. Theranostics

In recent years, theranostics as a novel concept, has attracted tremendous research interest, which is aimed at personalized medicine and real-time monitoring.^{119,120} In the personalized medicine of cancer, multitudinous treatment means and anti-cancer drugs have been put forward, and have made great progresses.¹²¹ Nevertheless, most anti-cancer drugs can not only combat cancers but also have high toxicity to normal cells and severe side effects. Furthermore, the therapeutic efficiency is dependent on the concentrations of effective drugs in the cancers. Therefore, real-time monitoring of drug delivery/release is also a vital issue in the construction of drug delivery systems.¹²² Meanwhile, an increasing number of nanomaterials have been applied in cancer theranostics, which have been engineered to acquire highly integrated personalized medicine and real-time monitoring in a single system. Recently, Dan and Chen *et al.* successfully developed a novel theranostic system based on Ta_4C_3 nanosheets for the combination of multiple imaging-guided therapy and photothermal therapy (PTT).⁴⁰ The detailed scheme of the preparation methods of $\text{MnO}_x/\text{Ta}_4\text{C}_3$ -SP composite nanosheets for theranostics is displayed in Fig. 6A. On the one hand, soybean phospholipid (SP), as a biocompatible natural amphiphilic molecule, could improve the dispersibility and biocompatibility of MXene-based materials. On the other hand, the manganese oxide (MnO_x) component could make MXenes desirable contrast agents for tumor microenvironment-responsive magnetic resonance (MR) imaging. Furthermore, Ta_4C_3 nanosheets are composed of tantalum element with high atomic number ($Z = 73$), which could be conducive for computed tomography (CT) imaging. Moreover, it is well known that most MXene-based materials possess high-efficiency photothermal conversion in

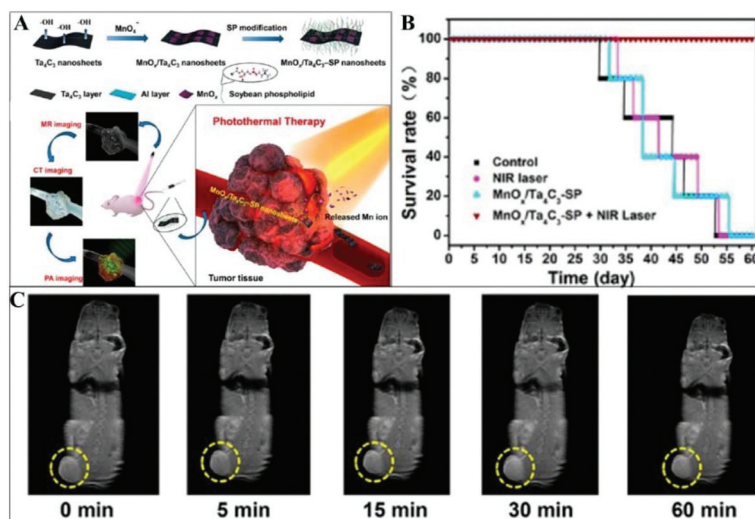


Fig. 6 (A) Schematic illustration of synthetic procedure and MR/CT/PA imaging-guided photothermal tumor therapy by MnO_x/Ta₄C₃-SP composites. (B) Survival rates of 4T1 tumor-bearing mice within the feeding duration after different treatments. (C) Corresponding T₁-weighted imaging of 4T1 tumor-bearing mice after i.v. administration of MnO_x/Ta₄C₃-SP composites for prolonged time intervals. Reprinted with permission.⁴⁰ Copyright 2018, American Chemical Society.

both the first and second NIR bio-windows. The photothermal-conversion performance of Ta₄C₃ nanosheets would endow them with the capability of photoacoustic (PA) imaging and photothermal therapy. Subsequently, the MnO_x/Ta₄C₃-SP composites would be used for investigating the therapeutic efficiency of photothermal ablation for mouse tumor xenografts. The tumor-bearing mice were randomly divided into five groups to receive different treatment and were cultured for 60 days. Thereinto, the group of MnO_x/Ta₄C₃-SP + NIR laser can remain healthy 60 days post treatment (Fig. 6B). These results could suggest the great therapeutic efficiency of PPT. In addition, it convincingly demonstrated the potential performance of MnO_x/Ta₄C₃-SP composite nanosheets in MR imaging (Fig. 6C). Hence, final MnO_x/Ta₄C₃-SP composites emerge as promising candidates for theranostics, which possess the multifunction of multiple imaging-guided therapy and PTT. Besides, Ti₃C₂ nanosheets have also been modified with manganese oxide (MnO_x) and biocompatible SP for further theranostics, which are also the combination of dual-modality imaging and PTT.¹¹⁰ In addition to multiple imaging-guided PPT, more methods and strategies to realize the combination of personalized medicine and real-time monitoring for theranostics based on MXenes should be developed.

3.5. Antibacterial

Bacteria are one of the main groups of organisms and also the largest number of a class of all creatures.¹²³ Also, bacteria can be found everywhere in air, water, and soil, which has a great impact on human activities. Nevertheless, some bacteria are pathogens for numerous diseases, which seriously harm human health.¹²⁴ Hence, various antibacterial nanomaterials have been developed for public health applications. Among many antibacterial materials, 2D nanomaterials including gra-

phene and MoS₂ have received multitudinous research interests due to their unique 2D structures.^{125–127} In general, the antimicrobial activities of graphene can be attributed to oxidative and physical stress induced by the sharp edges of graphene nanosheets, which may result in physical damage of cell membranes, thus leading to a loss of bacterial membrane integrity.^{128–131} Thus, MXene-based materials, as graphene-like nanomaterials, possess enormous potential in antibacterial applications. Rasool and Mahmoud *et al.* have proposed a report on the antibacterial behavior of MXene-based materials (Ti₃C₂) in colloidal suspensions.¹³² The detailed schematic diagram is displayed in Fig. 7A. Subsequently, Gram (+) *B. subtilis* and Gram (–) *E. coli* were cultivated with various concentrations of MXene-based materials (Fig. 7B). It is obvious that the quantity of bacterial colonies markedly decreases with increasing concentration of MXenes, suggesting the relevance of concentration and antimicrobial activity of MXenes. Furthermore, it also compared the bacterial cell viability exposed to MXenes with that of graphene oxide (Fig. 7C and D). Thereinto, MXenes show stronger antimicrobial activity than graphene oxide for both Gram (+) *B. subtilis* and Gram (–) *E. coli*. In addition, Rasool and Gogotsi *et al.* further utilized the antimicrobial activity of MXenes to facilitate sustainable water/wastewater treatment. As exhibited in Fig. 7E, Ti₃C₂ nanosheets are regarded as antibacterial membranes to modify onto polyvinylidene fluoride (PVDF) support.¹³³ Compared with the pristine PVDF support, fresh and aged Ti₃C₂/PVDF supports show massive dead bacteria, thus indicating outstanding antibacterial activity of MXenes. As mentioned above, MXenes possess better antibacterial activity than most traditional antibacterial nanomaterials. However, further cellular uptake and biocompatibility of MXene-based materials should also be intensively studied before their biomedical applications.

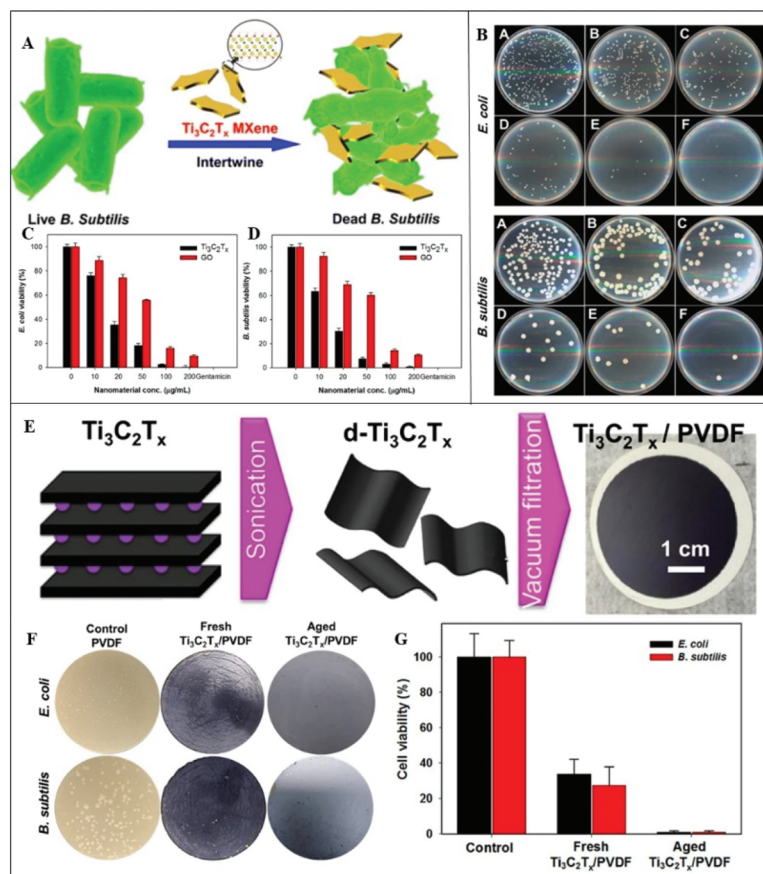


Fig. 7 (A) Schematic illustration of antibacterial activity of $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes. (B) Concentration dependent antibacterial activities of $\text{Ti}_3\text{C}_2\text{T}_x$ in aqueous suspensions. Cell viability measurements of (C) *E. coli* and (D) *B. subtilis* treated with $\text{Ti}_3\text{C}_2\text{T}_x$ and graphene oxide (GO) in aqueous suspension. Bacterial suspensions (10^7 CFU mL^{-1}) were incubated with different $\text{Ti}_3\text{C}_2\text{T}_x$ and GO concentrations (0–200 $\mu\text{g mL}^{-1}$) at 35 $^\circ\text{C}$ for 4 h at 150 rpm shaking speed. Reprinted with permission.¹³² Copyright 2016, American Chemical Society. (E) Schematic of $\text{Ti}_3\text{C}_2\text{T}_x$ membrane fabrication on a PVDF support. (F) Photographs of *E. coli* and *B. subtilis* growth on unmodified PVDF (control), and fresh and aged $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes coated PVDF membranes incubated at 35 $^\circ\text{C}$ for 24 h. (G) Cell viability measurements of *E. coli* and *B. subtilis* grown on fresh and aged $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes coated PVDF membranes for 24 h. Reprinted with permission.¹³³ Copyright 2017, Nature Publishing Group.

4. Cytocompatibility

It is well-known that MXene-based materials possess many excellent features, including large specific surface area, rich surface functional groups, outstanding electronic, mechanical, and physicochemical properties.¹³⁴ As introduced in previous sections, all these outstanding properties endow MXenes and related materials with great potential for various biomedical applications, such as biosensing, bioimaging, photothermal therapy, drug delivery, theranostic nanoplateform, and antibacterial activity. Nevertheless, the cytocompatibility of MXenes is the most crucial parameter for their potential in biomedical fields and should be evaluated and discussed first. Jastrzębska *et al.* have explored the cytotoxicity of most typical MXenes (Ti_3C_2) for cancerous (A549 and A375) and normal cells (MRC-5 and HaCaT) *in vitro*.²⁷ As shown in Fig. 8A, the suspensions of MXenes show greatest cytocompatibility in the case of HaCaT, which could maintain more than 70% cell viability in the whole range of tested concentrations. Moreover, it is obvious that MXenes would cause higher cytotoxic effects to

cancerous cells than to the normal ones. Furthermore, the ROS production of MXenes is the lowest for HaCaT cells than other groups, indicating that the possible mechanism of cytotoxicity of MXenes is attributed to ROS generation (Fig. 8B). In addition, most MXenes are fabricated using liquid exfoliation method from MAX phase. Thus, Chen *et al.* also explored the cytotoxicity of several kinds of common MAX phases ($(\text{Ti}_3\text{AlC}_2, \text{Ti}_3\text{SiC}_2, \text{and Ti}_2\text{AlN})$).²⁸ As displayed in Fig. 8C, all MXenes exhibited great biocompatibility for preosteoblast and the cells actively proliferated on all MXenes. Thereinto, Ti_2AlN exhibited the best cytocompatibility. More importantly, some previous reports also demonstrated that many parameters such as compositions, size, surface properties, and surface modification could influence the biocompatibility of nanomaterials. The development of different methods for the fabrication of MXene-based materials and various strategies for surface modification of MXenes could, therefore, potentially adjust the final outcome of toxicity. However, based on previous reports, we could find that the biocompatibility of MXene-based materials is still very limited and more attention should be

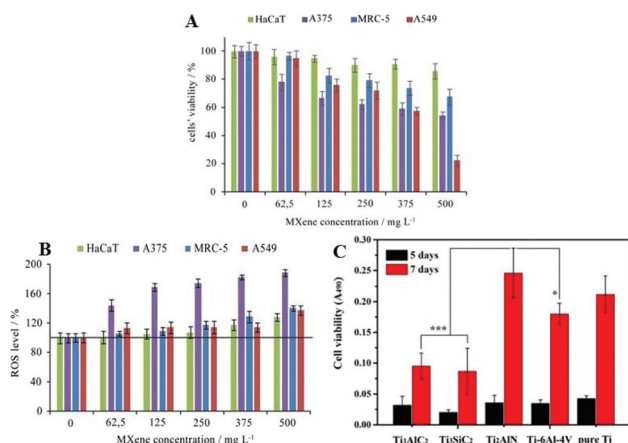


Fig. 8 (A) The results of MTT assay after 24 h exposure of A549, MRC-5, A375, and HaCaT cells to increasing concentrations of 2D sheets of Ti_3C_2 (the average viability SD; $n = 16$). (B) Production of reactive oxygen species (ROS) during incubation with various concentrations of 2D sheets of Ti_3C_2 (the average SD, $n = 16$). Reprinted with permission.²⁷ Copyright 2017, Elsevier. (C) MTS assay for the determination of cell viability after 5-day and 7-day incubation (Ti_3AlC_2 , Ti_3SiC_2 , Ti_2AlN , Ti-6Al-4V alloy, and pure Ti specimens). Reprinted with permission.²⁸ Copyright 2017, American Chemical Society.

focused on the systematical evaluation and adjustment of toxicity of MXene-based materials. The cell uptake behavior, cytotoxicity mechanism, *in vivo* distribution as well as *in vivo* toxicity of MXene-based materials should also be carefully examined before practical biomedical applications of MXene-based materials can be achieved.

5. Conclusions and outlook

In summary, MXene-based materials, as a new member of 2D materials, were first discovered by Gogotsi and colleagues in 2011. Being different from traditional 2D nanomaterials, the main compositions of MXenes include transition metal carbides, nitrides, and carbonitrides, which only need facile preparation methods with etching A layers of MAX at room temperature. Furthermore, it has been extensively reported that MXene-based materials possess multitudinous outstanding characteristics, such as large specific surface area, extremely low cytotoxicity, rich surface functional groups, and remarkable electronic, mechanical and physiochemical properties. Nevertheless, even with in-depth research on MXene-based materials, these excellent properties still cannot meet the requirements for various applications. Therefore, surface modification and functionalization are necessary for improving the properties of MXene-based materials. After surface modification, MXene-based materials have attracted much attention and have been extensively applied in multitudinous applications, including biomedicine, energy, and environment. Among these, the biomedical applications of MXene-based materials for biosensing, bioimaging, photothermal therapy, drug delivery system, theranostic nanoplateform, and

antibacterial agents have been summarized and discussed in this mini-review. Although surface modification and biomedical applications of MXene-based materials have attained some achievements, there still remain a large number of gaps in the development of surface modification and biomedical applications of MXene-based materials. For instance, hydrophilic polymers are usually utilized to modify MXene-based materials for improving water dispersity through non-covalent and physical adsorption interactions in most biomedical applications. However, non-covalent and physical adsorption interactions are not stable enough in some extreme cases. In addition, achievable control release is a crucial point for the construction of drug delivery systems. On the other hand, almost all drug loading strategies of MXene-based materials are through non-covalent interactions and physical adsorption, which cannot realize controlled release. Consequently, more surface modification strategies through covalent methods and formation of dynamic bonds are expected to be developed for conjugating polymers and controlled drug release systems in biomedical applications. Therefore, facile and efficient methods for surface modification should be developed to fulfill the requirements for biomedical applications. Finally, as emerging 2D materials with great potential in biomedical applications, only very few reports have examined the biocompatibility of MXenes *in vitro*. It is still at a very primary stage. The cell uptake behavior of MXene-based materials, and the influence of surface modification and properties of MXene-based materials on biocompatibility is still largely unknown. The information about the distribution, accumulation, clearance behavior as well as *in vivo* toxicity and long-term toxicity is lacking. In future, more attention and efforts should be focused on the development of novel and efficient methods for surface modification of MXenes to fulfill the requirements for biomedical applications, and in-depth investigation of biomedical applications and toxicity of MXenes and their composites. We believe this review article will largely promote the development of MXenes and related materials for biomedical applications.

Conflicts of interest

There are no conflicts to declare.

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