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REVIEW ARTICLE

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Recent advances and trends in the applications of MXene nanomaterials for tissue engineering and regeneration

Yongjin Zhong | Si Huang | Zeru Feng | Yu Fu | Anchun Mo

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department of Implantology, West China Hospital of Stomatology, Sichuan University, Chengdu, China

Correspondence
Anchun Mo, State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department of Implantology, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China.
Email: moanchun@163.com

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Abstract

MXene, as a new two-dimensional nanomaterial, is endowed with lots of particular properties, such as large surface area, excellent conductivity, biocompatibility, biodegradability, hydrophilicity, antibacterial activity, and so on. In the past few years, MXene nanomaterials have become a rising star in biomedical fields including biological imaging, tumor diagnosis, biosensor, and tissue engineering. In this review, we sum up the recent applications of MXene nanomaterials in the field of tissue engineering and regeneration. First, we briefly introduced the synthesis and surface modification engineering of MXene. Then we focused on the application and development of MXene and MXene-based composites in skin, bone, nerve and heart tissue engineering. Uniquely, we also paid attention to some research on MXene with few achievements at present but might become a new trend in tissue engineering and regeneration in the future. Finally, this paper will also discuss several challenges faced by MXene nanomaterials in the clinical application of tissue engineering.

KEYWORDS
bone repair, MXene, tissue engineering, tissue regeneration, wound healing

1 | INTRODUCTION

The traditional method of treating damaged tissue is organ transplantation, including autograft, and allograft. However, autograft is not only expensive but also risky, which is usually accompanied by side effects such as infection, inflammation and chronic pain; Allograft is limited by the lack of donor organs and may cause serious immune response.[1–3] The emergence of tissue engineering and regenerative medicine has overcome these problems.[4] As a branch of regenerative medicine, tissue engineering refers to the integration of materials science, chemistry, biology and engineering through cells, scaffolds and/or signal molecules.[5,6] At present, bone, skin, cardiovascular, neural tissue engineering are widely studied. To fully restore the morphology and biological functions of the damaged tissue, the selection of biomedical materials in tissue engineering is very significant.[7] Ideal tissue engineering materials can simulate the microenvironment of natural extracellular matrix, so as to improve the capacities of adhesion, proliferation, migration, differentiation and signal transmission of cells.[8,9]

In the last few years, the application of nanomaterials in the tissue regeneration has attracted extensive research interest. Based on nanotechnology, a variety of multifunctional biomaterials for tissue engineering and regeneration have been explored and developed, which can not only regulate cells growth as scaffolds, but monitor the process of tissue regeneration, control the release of drug, coordinate signal molecule transmission, and stimulate the mechanical properties of natural tissue.[10,11] Two-dimensional (2D) nanomaterial is the general term of a class of materials, including graphene, black phosphorus, MXene and so on, which has been extensively concerned since it was discovered. Thanks to its outstanding physicochemical performance (inherent optical property, unique 2D nanoplane and surface chemistry) and biological properties (excellent biocompatibility and biodegradability), the potential applications of a dozen of 2D materials in tissue regeneration have been widely explored.[2,12,13] In particular, MXene is an emerging class of 2D nanomaterials with several atomic layers and composed of transition metal carbides, nitrides or carbonitrides. The typical chemical formula of MXene is $M_{n+1}X_nT_x$, where M represents transition metal and X is carbon and/or nitrogen atoms, which are staggered with each other to form 2D nanoflakes. T indicates the terminal chemical group (—OH, —F, =O, etc.) attached to the surface of M layer during the production of MXene by chemical etching.[14–16] This new 2D nanomaterial with both atomic layers and abundant chemical functional groups, skillfully combining the metal conductivity of transition metal nitrides and carbides with the hydrophilicity terminal functional groups, is endowed with fascinating electronic, magnetic and optical properties.[17] Thanks to these performances, MXene has promptly become one of the high-profile materials in energy,[18] electronics,[19] environment[20] and other research fields, and many research groups have systematically reviewed and summarized it from different angles.[21–24] Currently, in the biomedical fields, compared with the research achievements of MXene nanomaterials and MXene-based composites in cancer treatment and diagnosis, biological imaging, sensing and drug delivery, their potential applications in tissue engineering are ignored.[25] As we know, MXene and MXene-based nanoplatforms possess excellent biocompatibility, biodegradability, photothermal property, antibacterial activity, targeted therapeutic performance, and electrical signal transmission ability, and are especially suitable for tissue engineering and regeneration.

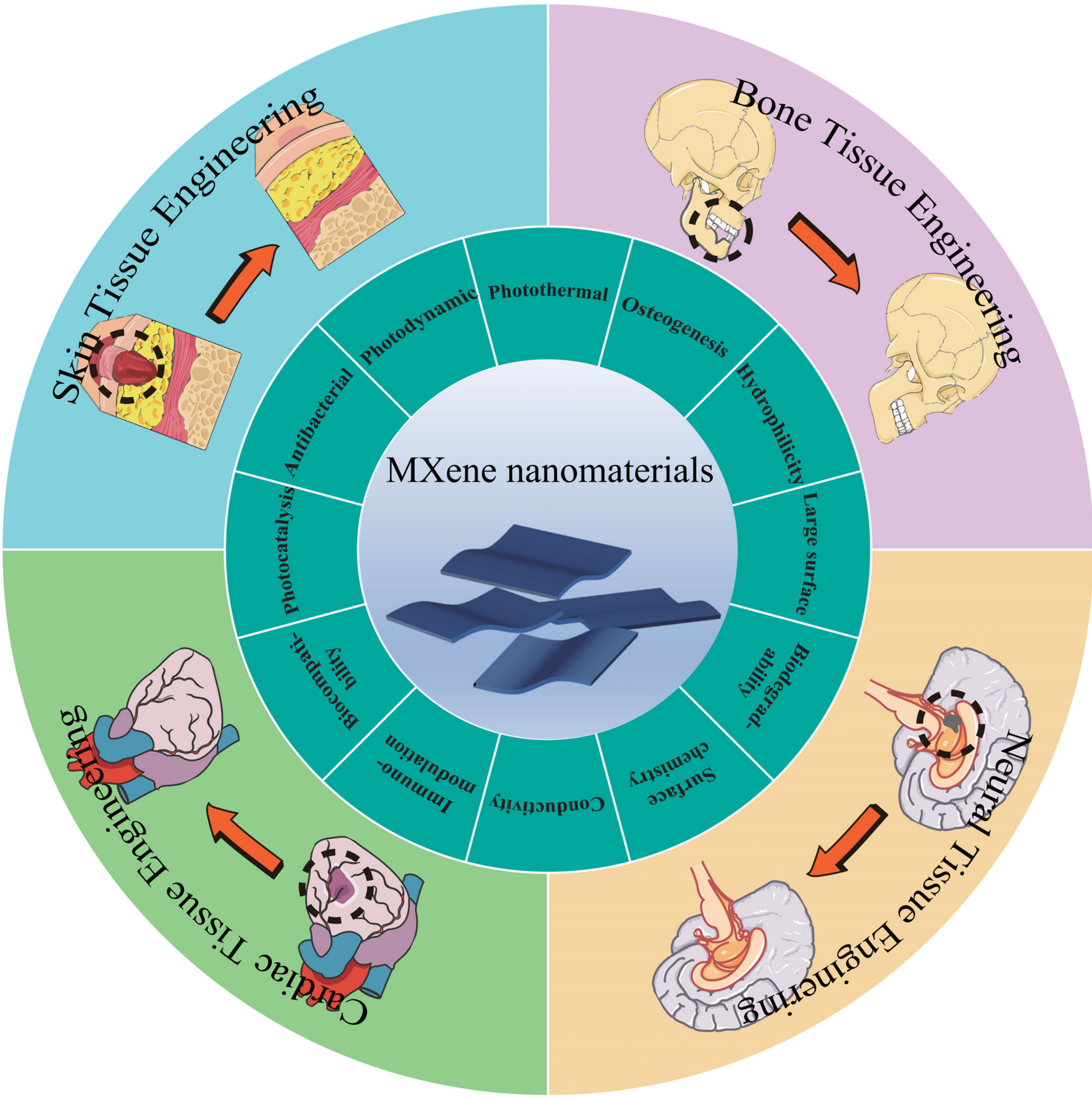

FIGURE 1 The properties of MXene (internal ring: antibacterial, photodynamic performance, photothermal performance, osteogenesis, hydrophilicity, biodegradability, surface chemistry, conductivity, immunomodulation, biocompatibility, and photocatalysis) and its applications in tissue engineering (outer ring: skin tissue engineering, bone tissue engineering, neural tissue engineering and cardiac tissue engineering).

Herein, we reviewed the application and development of MXene nanomaterials in tissue engineering in this work. First, the synthesis methods and surface modification of MXene were briefly introduced in the first part of the review. Second, we highlighted the recent application of MXene nanomaterials and their composites in tissue engineering such as skin wound healing, bone defect repair, neural tissue regeneration and myocardial tissue reconstruction, as illustrated in Figure 1. Then, we paid special attention to the new trends of MXene in tissue regeneration. In the end, the future prospects and challenges of MXene and MXene-based materials in the field of tissue engineering and regeneration were discussed. Compared with the previous publications,[25,26] this review clearly summarized the application and challenges of MXene in tissue engineering according to the different types of tissue. At the same time, we put forward the research hotspots and trends of MXene in the field of tissue regeneration with foresight.

2 | PREPARATION AND SURFACE MODIFICATION OF MXENE NANOMATERIALS

To date, there are many methods to synthesize 2D materials, including chemical vapor deposition,[27] hydrothermal syntheses,[28] electrochemical fabrication,[29] and molten salt etching.[30] In general, the synthesis of MXene can be categorized into top-down and bottom-up strategies.[31,32] Furthermore, most of the current preparation methods can endow MXene nanomaterials with abundant hydrophilic terminal groups such as —OH, —F, —O on the surface. Therefore, MXene displays excellent hydrophilicity, and appropriate surface modification can enhance its biocompatibility, stability, recyclability, loading capacity, biodegradability and other properties, undoubtedly increasing the application range of MXene-based materials in tissue regeneration.

2.1 | Synthesis of MXene

Top-down etching technology is a common approach for fabricating MXene, which involves the stripping of A layer in precursor MAX phase ceramics (Figure 2A,B).[33,34] This method is usually divided into two steps: (a) Etching MAX phase to acquire multilayer stacked MXene; In 2011, the use of hydrofluoric acid (HF) to manufacture MXene nanosheets was first discovered and reported in the research article of Gogotsi et al[35] Fluorine ions selectively and strongly combined with element A of MAX phase, destroying M-A bonds and resulting in the shedding of element A layer from MAX phase.[16] However, the fabrication of MXene with HF will cause irreversible damage to human body and environment, since high concentration of HF is strong corrosive. Instead of using relatively dangerous HF, some researchers etched Ti_3AlC_2 adopting a mild mixed solution of LiF and HCl at 40°C and successfully prepared $Ti_3C_2T_x$ MXene.[36] In another study, Halim et al. used 1 mol/L NH_4HF_2 as an etchant to etch Ti_3AlC_2

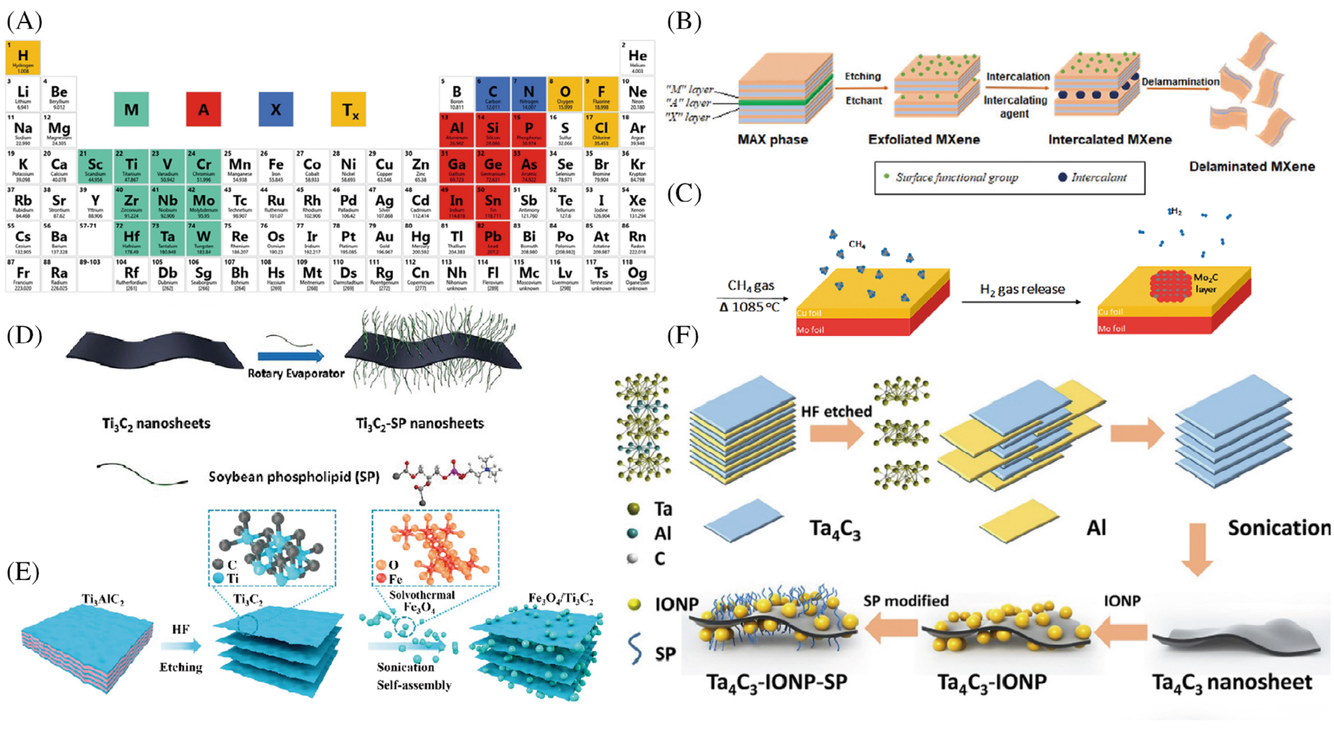

FIGURE 2 (A) The chemical elements that make up MXenes. Adapted with permission from Reference 34; (B, C) Schematic illustration of the synthesis methods of MXenes: (B) Top-down MXene synthesis process (acid exfoliation method); (C) Bottom-up methods (chemical vapor deposition). Adapted with permission from Reference 33; (D–F) Schematic illustrations of surface modification of MXenes: (D) Organic modification (SP modification of Ti_3C_2), Adapted with permission from Reference 45; (E) Inorganic modification (Fe_3O_4 modification of Ti_3C_2), Adapted with permission from Reference 49; (F) Organic–inorganic hybrid modification (IONP-SP modification of Ta_4C_3), Adapted with permission from Reference 55

films at room temperature, and also obtained $Ti_3C_2T_x$ nanosheets.[37] In recent years, a major breakthrough has been made in the preparation of MXene without fluorine. Some new technologies have sprung up, including hydrothermal method, electrochemical etching and molten salt synthesis. Li et al. proposed a technique for fabricating MXene nanomaterials by alkali assisted hydrothermal method.[28] They delightedly observed that multilayer $Ti_3C_2T_x$ could be produced by etching with sodium hydroxide solution at a high temperature of 270°C. Sun et al. successfully obtained Ti_2CTx MXene with —Cl, —O and —OH as terminal groups by electrochemical etching of Al from porous Ti_2AlC electrodes in dilute HCl.[29] In addition, researchers also reported for the first time that exclusive Cl-terminated MXenes were obtained via placing Max phase precursors in Lewis acid molten salts ($ZnCl_2$).[38] (b) Delaminating multilayer stacked MXene to obtain MXene nanosheets; The distances between MXene films can be increased by introducing insertion agents such as dimethyl sulfoxide, tetramethylammonium hydroxide and tetrabutylammonium hydroxide or sonication, making it easier to separate from each other, so as to gain few or single layered MXene nanoflakes.[33] Moreover, researchers successfully manufactured fluorine-free $Ti_3C_2T_x$ quantum dots by employing tetrabutylammonium hydroxide insertion agent and ultrasonic technology.[39]

Bottom-up technology is to control crystal growth at the atomic level to form 2D nanomaterials. The common bottom-up method is chemical vapor deposition (CVD). In the case of methane gas as raw material and Cu/Mo foil as substrate, ultrathin molybdenum carbide (MoC_2) was synthesized by CVD at 1085°C (Figure 2C).[27] In addition to CVD, template method and plasma enhanced pulsed laser deposition (PEPLD) also demonstrated great potential in the synthesis of 2D nanosheets. Joshi et al. prepared 2D hexagonal MoN nanosheets by using 2D MoO_3 as template in the heated NH_3 (800°C). They found that the obtained MoN perfectly reappeared the morphology of MoO_3.[40] Some scholars adopted PEPLD (using CH_4 plasma as carbon source, heating sapphire substrate to 700°C, and reacting with Mo vapor generated by pulsed laser) to form high-quality Mo_2C thin films.[41,42] Although compared with the traditional top-down technology, bottom-up technology is a simpler method to fabricate various high-quality ultrathin 2D materials, the bottom-up technology requires higher temperature conditions, coupled with the complex atomic morphology and structure of MXene nanomaterial, the bottom-up technology to generate MXene is still full of challenge.[33,43,44] In addition, no functional groups linked to the surface of MXene prepared by bottom-up technology, which limits the application of MXene in biomedical field.[27] In conclusion, how to use bottom-up technology to manufacture MXene nanomaterials safely and effectively still needs further study.

2.2 | Surface modification and functionalization of MXene

According to the category of modifier, there are three ways of surface modification/multi-functionalization of MXene nanomaterials:

1. *Organic modification*: The organic matter directly interacts with the surface structure of MXene and introduces new chemical functional groups after the reaction, effectively improving the dispersion stability, biocompatibility and reaction activity of MXene. The natural polymer soybean phospholipid (SP) can be bonded to the surface of MXene by physical adsorption (Figure 2D). The stability of modified MXene nanomaterial in dispersion is significantly enhanced, and it shows a long blood circulation time in mice.[45] Polyethylene glycol (PEG) is also adopted for modifying the surface of MXene. The addition of PEG can effectively improve the water dispersion of MXene materials.[46] Zhang et al. developed a honeycomb structure nanocomposite hydrogel consisting of polyacrylamide and Ti_3C_2, which contributed to drug delivery and release.[47]
2. *Inorganic modification*: Inorganic modification usually selects inorganic nanomaterials to functionalize MXene. On the one hand, the modification method can availably prevent the stacking of MXene nanoflakes, on the other hand, it can endow MXene nanomaterials with unique optical, electrical, magnetic and other properties. Zhu et al. explored the electrochemical responses of MXene doped with metal ions to coexisting CD^+, Pb^+, Hg^+, and found that its sensitivity was better than most previous reports.[48] In one investigation, scholars synthesized the Fe_3O_4/Ti_3C_2 MXene composite via a facile method, of which the hybrid was confirmed possesses outstanding nonlinear optical properties (Figure 2E).[49] Furthermore, Ti_3C_2@Au composite was obtained by in-situ growth, which realized the dual imaging function of photoacoustic (PA) imaging and computed tomography (CT).[50] Dai et al. loaded MnOx nanoparticles on Ta_4C_3 MXene. Due to the high light conversion efficiency of $Ta_4C_3T_x$ and the MRI characteristics brought by MnO_x, the composite can be used as a trimodal imaging MR-CT-PA nanoplatform to guide tumor photothermal therapy in NIR- I window.[51]
3. *Organic–inorganic hybrid modification*: The organic–inorganic hybrid modification method absorbs the advantages of organic and inorganic modifications, and possess greater flexibility in the surface modification engineering of MXene nanomaterials and make MXene surface more functional, enriching the properties of MXene. Liu and his colleagues integrated DOX into Ti_3C_2-Co composite, achieving accurate drug release controlled by magnetic targeting and thermal response.[52] A study reported a metal–organic framework composed of MXene/carbon nanohorns/β-cyclodextrin. They found that the material could be used as an electrochemical sensor to detect carbendazim pesticide residues in food.[53] Ta_4C_3-IONP-SPs nanocomposite can accumulate in cancer cells, thereby, it can serve as a contrast agent for imaging technology (Figure 2F).[54,55]

3 | APPLICATIONS OF MXENE NANOMATERIALS IN TISSUE ENGINEERING AND REGENERATION

After surface modification and functionalization, MXene has been endowed with more excellent physical and chemical characteristics, and has been extensively studied in the biomedical field. In the following, we will focus on the application of MXene in skin, bone, nerve, and myocardial tissue engineering.

3.1 | MXene nanomaterials for skin tissue engineering and regeneration

Skin trauma is the destruction of skin integrity under the action of external mechanical forces and other factors, resulting in skin tissue disconnection or defect. Wound healing, containing three stages of inflammation, proliferation and remodeling, is a continuous and complex dynamic repair process, which will often be affected by infection.[56,57] When the wound is infected, a large number of toxins and enzymes are secreted by bacteria to dissolve the matrix and cellulose in the skin tissue, aggravating the tissue damage.[58,59] Hence, the prevention and treatment of infection is the key step to accelerate wound healing.

Currently, researchers have been exploring the antibacterial activity of MXene nanomaterials. Some scholars studied the antibacterial performance of $Ti_3C_2T_x$ MXene against *Escherichia coli* and *Bacillus subtilis*, and discovered that it had good antibacterial effects on both bacteria.[60] In another study, researchers revealed that the antibacterial efficacy of $Ti_3C_2T_x$ MXene against *E. coli* and *B. subtilis* depends on their size and exposure time.[61] Also, several scholars added $Ti_3C_2T_x$ MXene to the chitosan-hyaluronate matrix and they observed the nanocomposites containing 5 and 10 wt% MXene visually inhibited the growth of *Staphylococcus aureus* and *E. coli*.[62] Mayerberger et al. introduced a method of preparing electrospun $Ti_3C_2T_x$ MXene/chitosan nanofibers as an infectious wound bandage.[63] The results of antibacterial experiment in vitro demonstrated that the *E. coli* and *S. aureus* colonies in culture dishes were reduced by 95% and 62% respectively, which suggested that MXene/chitosan nanofiber was a very ideal candidate for wound dressing. Zhou et al. constructed a multifunctional scaffold platform with outstanding self-healing ability and conductivity using $Ti_3C_2T_x$ MXene nanosheets as the key component, which can especially restrain the survival of multidrug-resistant bacteria (MRSA) and destroy cell membrane.[64] In addition, different MXene materials exhibit different bactericidal abilities. Through comparing the antibacterial properties of Ti_2C and Ti_3C_2 against *E. coli*, the researchers noticed that Ti_3C_2 MXene had an evidently effect on bacterial activity, yet there was no significant antibacterial activity for Ti_2C MXene.[65]

In light of the excellent antibacterial effect of MXene nanomaterials, it is a very promising strategy to use them for skin tissue engineering. In the following, we will summarize the research on the MXene to facilitate wound healing in recent years from different perspectives.

3.1.1 | MXene acts as a photodynamic agent for wound healing

Photodynamic therapy is an emerging method to treat infectious wounds.[66,67] It uses photosensitizer to produce reactive oxygen species (ROS) through photodynamic reaction to disrupt the cell membrane structure to achieve the purpose of antibacterial.[68] Considering the outstanding photocatalytic efficiency of MXene, some scholars bound MoS_2 and Ti_3C_2 MXene together to form a special 2D bio-heterojunction (bio-HJ) that can accelerate the separation of electrons and holes and generate a large number of ROS inside and outside bacteria.[69] Remarkably, Ti_3C_2 MXene/MoS_2 2D bio-heterojunction was demonstrated to promote fibroblast migration and had excellent anti-inflammatory, angiogenesis and re-epithelization capacities. A MZ-8/PLA electrospun membrane with photothermal and photodynamic properties was reported by Zhang's group. Coincidentally, this multifunctional platform can provoke the emergence of ROS to accelerate the closure of bacterial invasive wounds, and its bactericidal rates to *E. coli* and MRSA reached 99.9% and 99.8% respectively.[70] Undeniably, normal skin tissue may also be damaged by a large amount of ROS. A polyvinylpyrrolidone (PVP)-functionalized Nb_2C nanosheet (Nb_2C-PVP NSs) was reported in a recent study. Scientists noted that the Nb_2C-PVP composite was endowed with satisfactory antioxidant properties, which could reduce the amount of ROS, and increase the activity of normal cells.[71] Yang et al. decorated the MXene-based composite structure with fibroblast growth factor-21 to improve its biosafety, which prevented the continuous damage of ROS produced by the structure to normal tissues and facilitated the reconstruction and regeneration of infectious skin damaged tissue.[69]

3.1.2 | MXene acts as a photothermal agent for wound healing

Under the stimulation of thermotherapy, bacteria are cleaved and the development of a variety of pathogenic microorganisms is hindered. Simultaneously, mild heating can facilitate cell proliferation and angiogenesis, which is conducive to repairing and remodeling damaged tissues.[72] In particular, MXene nanomaterial acts out efficient photothermal conversion with the near-infrared laser irradiation. Herein, the development of photothermal agent based on MXene to facilitate the healing of infected wounds has attracted more and more attention. Remarkably, the integration of silver nanoparticles (Ag NPs) and $Ti_3C_2T_x$ MXene demonstrates a synergistic antibacterial effect.[73] The novel composite with NIR irradiation had a brilliant killing effect on *S. aureus* and *E. coli*, suggesting that Ag/ $Ti_3C_2T_x$ can be used as a prominent photothermal antibacterial treatment platform to control wound infection and quickly narrow the damage scope (Figure 3A–C).[73] Xu et al. mixed amoxicillin (AMX), MXene and polyvinyl alcohol (PVA) and electrospun them into MXene-AMX-PVA nanofiber membrane as wound dressing for antibiotic and photothermal synergistic antimicrobial to recover infectious wounds.[74] Under NIR irradiation, the heat generated by MXene can suppress bacterial proliferation and facilitate the release of AMX, which enormously improve the healing rate of infectious wounds in mice.[74] Li et al. propose a muscle-inspired MXene/PVA hydrogel with high toughness and photothermal effect. The MXene/PVA hydrogel can obviously accelerate the proliferation of fibroblasts. When exposed to NIR

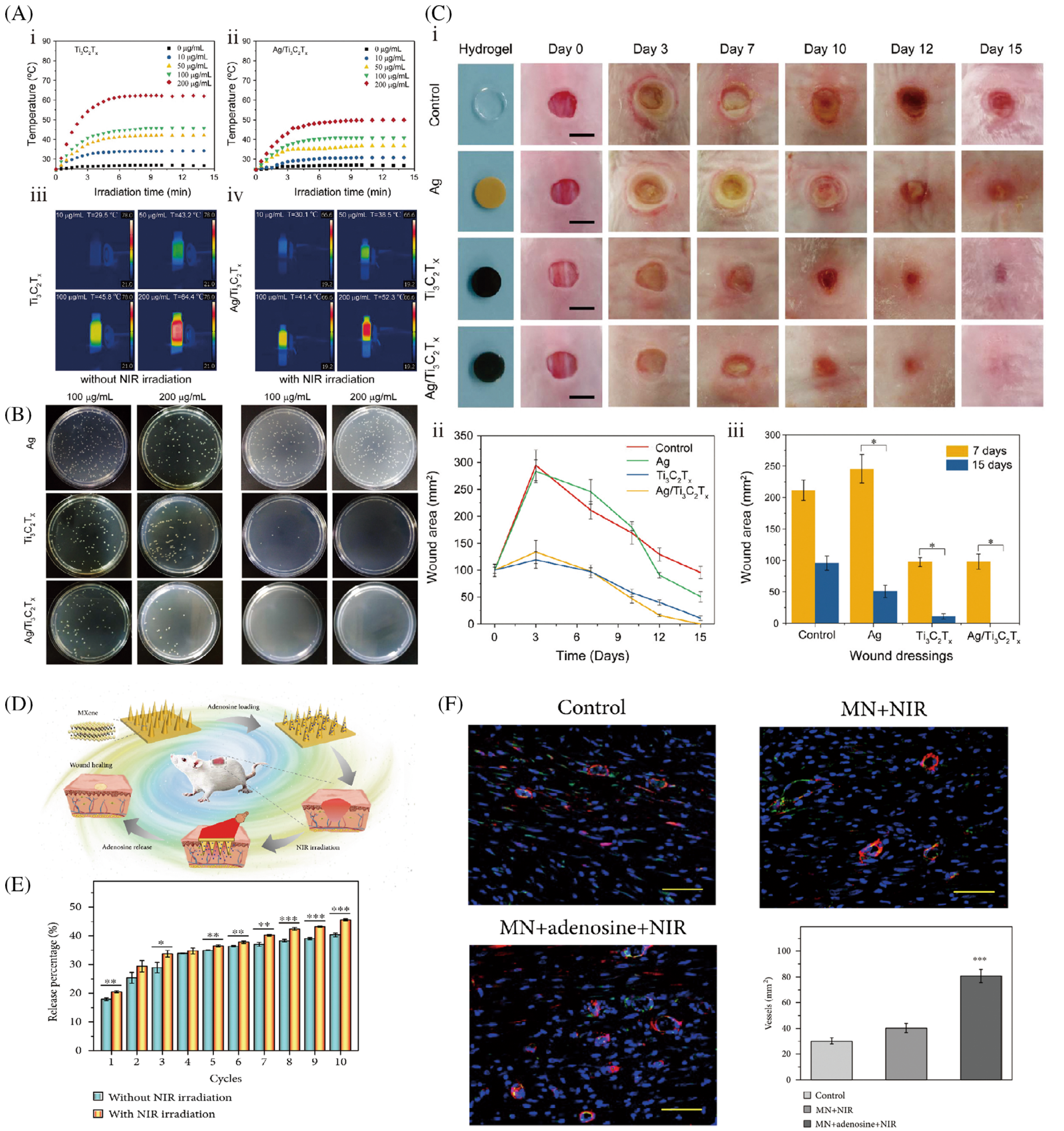

FIGURE 3 (A) Temperature changes of suspensions containing different concentrations of (I) $Ti_3C_2T_x$ and (ii) $Ag/Ti_3C_2T_x$ and the thermal images of (iii) $Ti_3C_2T_x$ and (iv) $Ag/Ti_3C_2T_x$ under 808 nm NIR irradiation, separately; (B) Optical photos of bacterial colonies formed without/with 808 nm NIR irradiation; (C) Wound healing characteristics. (i) Photographs of wound healing on days 0, 3, 7, 10, 12, 15. (ii) The wound area curves of different groups during Day 0–15. (iii) The wound size of different groups on Day 7 and Day 15 (*p < .05, **p < .01, ***p < .001); Adapted with permission from Reference 73; (D) Schematic illustration of MXene-integrated microneedle patches with adenosine encapsulation for wound healing; (E) The cumulative release of adenosine from PBA-integrated hydrogel with/without 10 cycles of NIR irradiation; (F) Immunofluorescence staining showing the neovascularization situation and the quantification of vascular structures. $CD31^+$ structures (green) and α-smooth muscle Actin-positive cells (red). (*p < .05, **p < .01, ***p < .001). Adapted with permission from Reference 81.

irradiation, this composite hydrogel could accelerate granulation tissue formation, collagen deposition, and scar free tissue formation.[75] A wearable wound dressing was designed via depositing a layer of $Ti_3C_2T_x$ nanosheet coating on cellulose fiber nonwoven fabric.[76] When it was applied to the wound skin tissue of rats, the immunohistochemical results manifested that the bacteria in the infected wound area disappeared, the inflammation was weakened, the injury was gradually repaired, and no obvious toxicity to the lungs and kidneys of rats was noticed.

Drug intervention is also one of the methods to accelerate wound healing. Via taking full advantage of the photothermal effect of MXene, the controllable release of drugs can be realized. Jin et al. fabricated temperature responsive MXene nanobelts carrying vitamin E, which can facilitate vitamin E release to accelerate wound healing under NIR irradiation.[77] Analogously, Yang et al. presented a MXene-based hydrogel as intelligent drug delivery system. With the splendid NIR absorption capacity, the Ag NPs in the hydrogel can be released to the depth of the wound to reduce inflammatory responses and boost the formation of new blood vessels.[78] Moreover, microneedle, as a painless and noninvasive drug delivery system, has been widely studied and applied in skin tissue regeneration.[79,80] Sun et al. matches MXene and microneedle patch to form a multifunctional platform (Figure 3D–F), which realizes the active and controllable release of drugs (adenosine) in the microneedle system via taking advantage of the photothermal effect of MXene to promote angiogenesis in skin wound.[81].

3.1.3 | MXene acts as a conductive material for wound healing

Previous studies have proved that electrical stimulation can promote angiogenesis, improve blood circulation, regulate cell proliferation and differentiation, and arouse tissue remodeling in the process of trauma recovery.[82–84] Owing to the distinct conductivity of MXene, there are grounds to believe MXene-based nanomaterials can actively adjust the growth of skin cells and drive skin tissue regeneration. Mao et al. proposed to synthesize MXene and regenerated bacterial cellulose (rBC) into composite hydrogels as wound dressings through physical and chemical dual cross-linking.[85] In the rat full-thickness skin defect model, rBC/MXene showed better wound healing ability than the existing dressings. Remarkably, under the electrical stimulation, rBC/MXene composites can inhibit inflammation, up-regulate the expression of VEGF and other related genes, induce re-epithelialization of skin wound, drive collagen synthesis, promote blood vessel growth, motivate granulation tissue formation, and accelerate wound closure.[85] A multifunctional scaffold with $Ti_3C_2T_x$ MXene nanosheets as important raw materials was developed by Zhou's team, which has splendid tissue adhesion and electrical conductivity.[64] They evaluated the healing ability of the scaffold on MRSA-infected wounds. Under its influence, the infection range of MRSA at the wound is reduced, the collagen deposition is increased, and the differentiation of vascular endothelium is enhanced, which greatly shortens the time of MRSA infected wound healing. Furthermore, the scaffold is endowed with good hemostatic ability specifically manifested in the notable reduction of bleeding volume and coagulation time, suggesting that the MXene-based scaffold can quickly stop bleeding and form blood clots in the early stage of wound healing, so as to restore the wound.[64] Conductive MXene nanomaterials are also used for the management and supervision of wound areas. Some researchers have integrated MXene based-electronics into microneedle dressing to constantly monitor the movement of the wound area, consequently, to remind patients to avoid the risk of long-term difficult-to-heal wounds caused by frequent muscle stretching.[86]

3.2 | MXene nanomaterials for bone tissue engineering and regeneration

Trauma, tumor resection, infection, and congenital malformation are the primary factors causing bone defect.[87–89] However, it is difficult to reconstruct large bone defects due to the limited ability of human bone tissue repair, herein bone regeneration or replacement has been verified to be an effective method of current treatment of bone loss or defects.[90] In recent 10 years, although some biomedical materials such as beta-tricalcium phosphate (β-TCP), hydroxyapatite (HA) and their composites have made great progress in bone tissue engineering,[91] while their shortages in bearing capacity, osteogenesis, osteoconductivity, osteoinductivity, and biodegradability still need to be improved.

As a member of the 2D material family with splendid properties, MXene has great potential in bone tissue engineering. To date, many scholars have made numerous efforts in MXene nanomaterials mediating the proliferation and early differentiation of cells. Researchers assessed the osteogenic activity of MXene on human Mesenchymal Stem Cells (hMSCs) with cell culture medium containing different concentrations of MXene.[92] When the concentration was <20 μg/ml, hMSCs showed distinct proliferation and osteogenic differentiation activity. Moreover, the rising expression of early osteogenic genes RUNX2 and OPN and late osteogenic gene BSP was also observed under the stimulation of MXene. As we know, cell spheroids provide a 3D cell culture environment that mimics the in vivo microenvironment to strengthen the vitality and function of the cells in the spheroids.[93,94] At present, this kind of cell spheroid has attracted extensive attention in the field of tissue engineering. Jang et al. ingeniously used MXene nanoparticles as cell adhesive to quickly form hMSC spheroids. It was found that the spheroids could promote the osteogenic differentiation of hMSCs, and showed significant ALP activity and active mineralization without osteogenic medium.[95] Zhang et al. reported that a multilayer MXene film improved the adhesion, proliferation and osteogenic differentiation of mouse preosteoblasts (MC3T3-E1) in vitro.[96] In another study, polycaprolactone MXene (PCL-MXene) composite electrospun fibers were synthesized for the first time,[97] on which MC3T3-E1 showed great cell viability. Furthermore, calcium phosphate minerals conducive to osteogenesis can precipitate qualitatively and quantitatively on the composite fibers, which may be due to the wettability of MXene nanomaterials. Huang et al. invented Ti_3C_2 MXene/poly(L-lactic acid) composite nanofibers for BMSCs culture.[98] Similarly, the nanofibers could also facilitate the growth and extension of BMSCs and facilitate the differentiation of BMSCs into osteoblasts to improve the osteogenic effect. Yin et al.

adopted MXene-based composite as substrates to culture MC3T3-E1 to recognize whether MXene possess the potential to promote bone formation.[99] It was found that the expression of ALP increased after 14 days, indicating that osteogenic potential of MC3T3-E1 was activated. Subsequently, calcium nodules were gradually densely distributed on the surface of the complex, manifesting that the cells had reached the late stage of bone differentiation and the extracellular matrix was mineralized.[99]

How does MXene promote the adhesion and growth of osteogenic-related cells through the cell-material interaction and the potential biological mechanism? (1) Improve the physical and chemical properties of the substrate material surface. It was found that the material surface with good hydrophilicity has a significant stimulating effect on the biological behavior of cells, such as adhesion and proliferation.[100] The composite nanofibers doped with Ti3C2 MXene can supply the hydrophilic functional groups required for the adhesion of BMSCs.[97,98] Furthermore, the coating modified by 2D graphene could increase the roughness of the original substrate, and the wrinkled nanotopography provided more attachment sites for cell adhesion.[101] (2) Adsorb the surrounding proteins. The large surface area and negatively charged oxygen-containing groups of 2D nanomaterials can absorb the proteins with positive charge through strong electrostatic reactions. On the one hand, proteins can increase the hydrophilicity of the material surface. On the other hand, the RGD sequence of proteins (arginine glycine aspartate sequence) can be as ligands to specifically bind to the integrin of the filamentous pseudopodia of cells, thereby promoting the adhesion and anchoring of cells on the material surface.[102–104] (3) Regulate the signaling pathways. An experiment showed that the Wnt/β-catenin signaling pathway was involved in the process of 2D material graphene promoting BMSC proliferation and osteogenic differentiation.[105] In another study, Ti_3C_2Tx MXene nanoflakes can facilitate the osteogenic differentiation of hPDLC, thereby accelerating the regeneration of periodontal tissue. It was further found that its potential mechanism may involve the regulation of HIF-1α/Wnt signaling pathway.[106] Moreover, researchers also observed that 2D nanomaterial graphene oxide can enhance the phosphorylation level of Erk1/2, which can stimulate the expression of downstream VEGF and BMP - 2, thereby promoting angiogenesis and new bone formation.[107]

Taken together, MXene has great potential in mediating cells into osteogenic differentiation. Therefore, the addition of MXene nanomaterials can further improve the osteogenic properties of existing substrate materials. At present, numerous scholars have sedulously used MXene as scaffold material, coating material, barrier membrane and so on to around bone regeneration in vivo (Table 1), and has achieved satisfactory results in these fields.

3.2.1 | MXene nanomaterials as a coating

The close integration between implants and surrounding bone tissue is the key to the success of implant surgery. Osseointegration is constantly influenced by the physicochemical properties of the implant surface.[108–111] Owing to the eye-catching biocompatibility of titanium (Ti) and its alloys, they are widely applied in bone tissue engineering.[112] However, the fly in the ointment is that pure Ti lacks the ability to stimulate osteogenesis and mainly relies on mechanical locking with alveolar bone to provide retention. The introduction of coating can change the surface physicochemical properties of implants and enhance and improve the interaction between implants and bone tissue. Jang's group evenly wrapped Ti_3C_2 MXene on the titanium surface adopting electrophoretic deposition technique.[113] Their experimental results exhibited the osteoinductive capacity and the osteogenic differentiation activity were notably strengthened due to the MXene coating layer. In addition to enhancing osteogenic capacity, MXene can also inhibit osteolysis. The fragments and particles caused by implant would accumulate in the bone-implant interface, resulting in the aseptic loosening of implant.[114,115] A recent study reported an antioxidant based on few-layered Nb_2C MXene.[116] By scavenging ROS, few-layered Nb_2C MXene effectively prevents the emergence of inflammatory factors and the activation of osteoclasts. The osteolytic bone resorption on the skull surface decreased apparently in the mouse model after being injected few-layered Nb_2C. These results prompted few-layered Nb_2C MXene may be a promising implant coating material to prevent the appearance of osteoclasts and per-implant osteolysis. Moreover, a momentous point is that peri-implant infection would postpone osteointegration and lead to aggressive bone resorption by provoking excessive pro-inflammatory cascade reactions.[117–119] Avoiding implant area from infection therefore is essential, and adding a layer of antibacterial coating on the implant surface is a good choice to resolve the problem. A medical Ti plate coated with Nb_2C MXene nanosheets (Nb_2C@TP) has been designed to control pre-implant infection,[120] in which Nb_2C MXene plays the role against bacteria and biofilm due to its inherent bactericidal and photothermal effect. Nb2C MXeneNb$_2$C@TP can down-regulate the energy metabolism related pathways of bacteria and inhibit the formation of bacterial biofilm. Furthermore, in the mouse infection model, Nb_2C@TP not only eliminated bacteria, but also significantly reduced the generation of ROS in inflammatory responses under the irradiation of NIR, which remarkably accelerated angiogenesis and tissue remodeling of the infected areas.[120] Yin et al. prepared a multifunctional coating on insert orthopedic material, which was composed of tobramycin (TOB)-laden Ti_3C_2 MXene and gelatin methacrylate (GelMA) hydrogels.[99] In this composite coating, Ti_3C_2Tx-based MXene nanosheets can inhibit bacterial growth through direct contact. At the same time, Ti_3C_2 has a large surface with lots of negatively charged terminal groups (—F, —OH, and =O), which can adsorb the antibacterial agent TOB through electrostatic binding and continuously release it in the lesion area. Taken together, the synergistic bactericidal effect of Ti_3C_2 nanosheets and TOB provides a sterile environment for postoperative bone tissue reconstruction. Moreover, osteoblasts displayed cell adhesion, spreading capacity and ALP activity on the coating. When introducing the multifunctional coating into Sprague–Dawley rats with femoral condyle defect model, more bone deposition and new bone formation around the implant were detected, revealing its marvelous ability of osteoinductivity and osteointegration.[99]

TABLE 1 MXene nanomaterials in the applications of bone tissue engineering.

MXene type	Modification/composites	Form of application	Study type	Results	References
Ti_3C_2	PCL (MXene/PCL nanofibers)	—	In vitro	Enhanced the cell viability of preosteoblasts (MC3T3-E1)	97
Ti_3C_2	PLLA-PHA (MXene/PLLA-PHA nanofibers)	—	In vitro	Enhanced BMSC's differentiation to osteoblasts	98
Ti_3C_2	—	Coating	In vitro	Enhanced BMSC osteogenic differentiation	113
Nb_2C	—	Coating	In vivo	Killed bacteria, mitigated excessive inflammatory responses and promote angiogenesis	120
Ti_3C_2	SP + TOB + GelMA (SP@MX-TOB/GelMA)	Coating	In vivo	Killed bacteria, enhanced osteogenicity, osseointegration and ablated residual osteosarcoma cells	99
Ti_3C_2	PLA (OTES-Ti3C2Tz/PLA)	GBR membrane	In vitro	Strengthened osteogenic differentiation of MC3T3-E1 preosteoblasts	124
Multilayered Ti_3C_2	—	GBR membrane	In vivo	Promoted early osteogenesis, mineralization and bone regeneration	96
Ti_3C_2	UHAPNWs (MXene/UHAPNWs)	GBR membrane	In vivo	Facilitated bone regeneration	125
Ti_3C_2	—	—	In vivo	Activated WNT/HIF-1α-Mediated Metabolism Reprogramming for Periodontal Regeneration	106
Ti_3C_2	BGS (MXene/BGS)	Scaffold	In vivo	Augmented osteosarcoma phototherapy and accelerated bone tissue reconstruction	136
Nb_2C	Mesoporous Silica layer + BG + SNO (MS/MXene-BG-SNO)	Scaffold	In vivo	Enhanced osteosarcoma ablation, bone regeneration, and vascularization	137
Nb_2C	BGS (MXene/BGS)	Scaffold	In vivo	Enabled photothermal ablation of osteosarcoma and facilitated bone regeneration	140
Nb_2C	Mesoporous silica layer + R837 + BG (BG@NbSiR)	Scaffold	In vivo	Inhibited growth/metastasis of breast cancer to bone and accelerated bone defect repair	146
Few-layered Nb_2C	—	—	In vivo	Decreased the production of cytokines and inhibited osteoclastogenesis	116
Ti_3C_2 MQDs	—	—	In vitro	Promoted immune tolerance of transplanted cells while supporting BMSCs survival and proliferation.	168

Abbreviations: BG/BGS, bioactive glass/bioactive glass scaffold; GelMA, gelatin methacrylate; MQDs, MXene quantum dots; OTES, n-octyltriethoxysilane; PCL, polycaprolactone; PHA, poly(hydroxyalkanoate); PLA, poly(lactic acid); PLLA, poly(ʟ-lactic acid); R837, an immune adjuvant; SP, polyetheretherketone; TOB, tobramycin; UHAPNWs, ultralong hydroxyapatite nanowires.

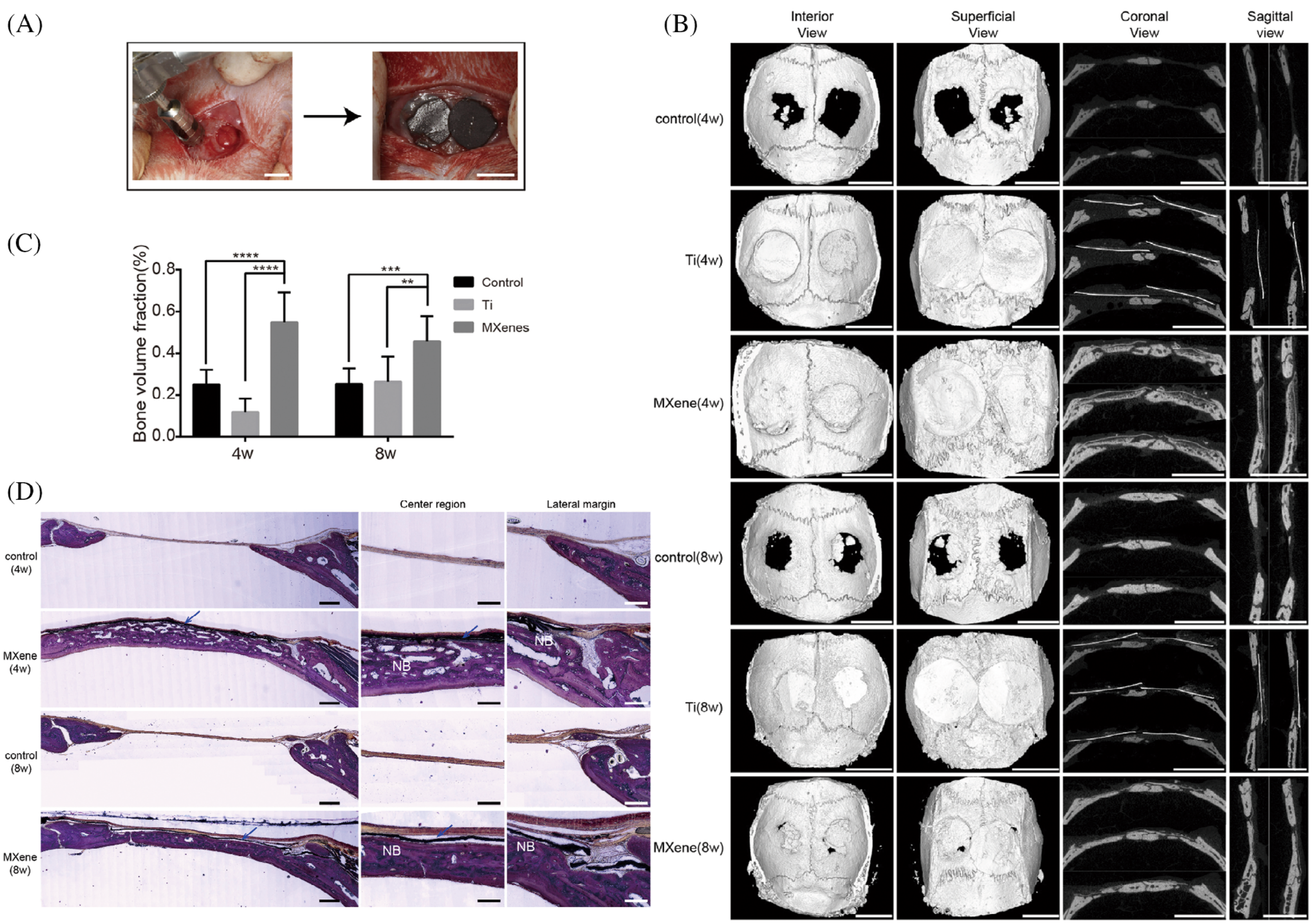

FIGURE 4 (A) Surgical operation to create rat calvarial defect model and to cover the bone defects with MXene films. (B) Micro-CT reconstruction images of bone defect samples including interior, superficial, coronal and sagittal views at the 4th and 8th week after surgery. (C) Bone volume fraction (BVF) at 4 and 8 weeks after surgery. (***p* < .01, ****p* < .001, and *****p* < .0001). (D) Undecalcified histological sections of calvarial samples 4 and 8 weeks after surgery following Van Gieson's staining. Adapted with permission from Reference 96.

3.2.2 | MXene as a guided bone membrane

Guided bone regeneration (GBR) is most primary mean to solve periodontal bone loss and the defects of bone around implants.[121,122] The ideal GBR would form a bioactive barrier between soft tissue and bone defect to create a closed environment, so that osteogenic precursor cells can enter the bone defect areas first, grow preferentially and regenerate bone tissue.[122] Currently, biodegradable membrane has been a common GBR membrane since it can avoid the secondary surgery and reduce the risk of patients' pain and postoperative complications. However, the shortcomings of rapid degradation, poor antibacterial effect and weak mechanical properties restrict the further application of biodegradable membrane.[123] In view of the superior physicochemical properties and biological characteristics of MXene nanomaterials, developing a guided bone regeneration membrane based on MXene with superior mechanical properties, biocompatibility, biodegradability, and osteoinductive potential is a hotspot at present. Zhang et al. carried out the study of multilayered $Ti_3C_2T_x$ MXene films for GBR.[96] They found that the GBR membrane adhered well to the tissue around bone defect area because of the splendid hydrophilic surface of MXene films. After MXene membrane was implanted subcutaneously in rats with skull defects for 4 weeks, the defect spaces under MXene membrane were almost filled with uniform and continuous new bone without obvious inflammatory reactions, meaning that MXene membrane has excellent osteoinductivity and osteogenesis (Figure 4). A nanocomposite film was prepared by embedding $Ti_3C_2T_x$ nanosheets into PLA matrix.[124] Compared with pure PLA membrane, the introduction of $Ti_3C_2T_x$ MXene not only increased the mechanical properties of the composite membrane, but also improved the in vitro adhesion, proliferation and osteogenic differentiation of MC3T3-E1. Fu et al. have studied the potential of nanocomposite membrane consisting of $Ti_3C_2T_x$ nanosheets and ultralong hydroxyapatite nanowires (UHAPNWs) to induce bone regeneration.[125] The results of animal experiments showed there was no distinct fibrous tissue around UHAPNWs/MXene composite membrane, and the whole of skull defect area was full of layered bone formed of vascular channels and bone cavities. Furthermore, severe periodontitis can cause alveolar bone absorption and defect, resulting in tooth loosening and loss.[126,127] Because the reconstruction of alveolar bone depends on the proliferation and differentiation of

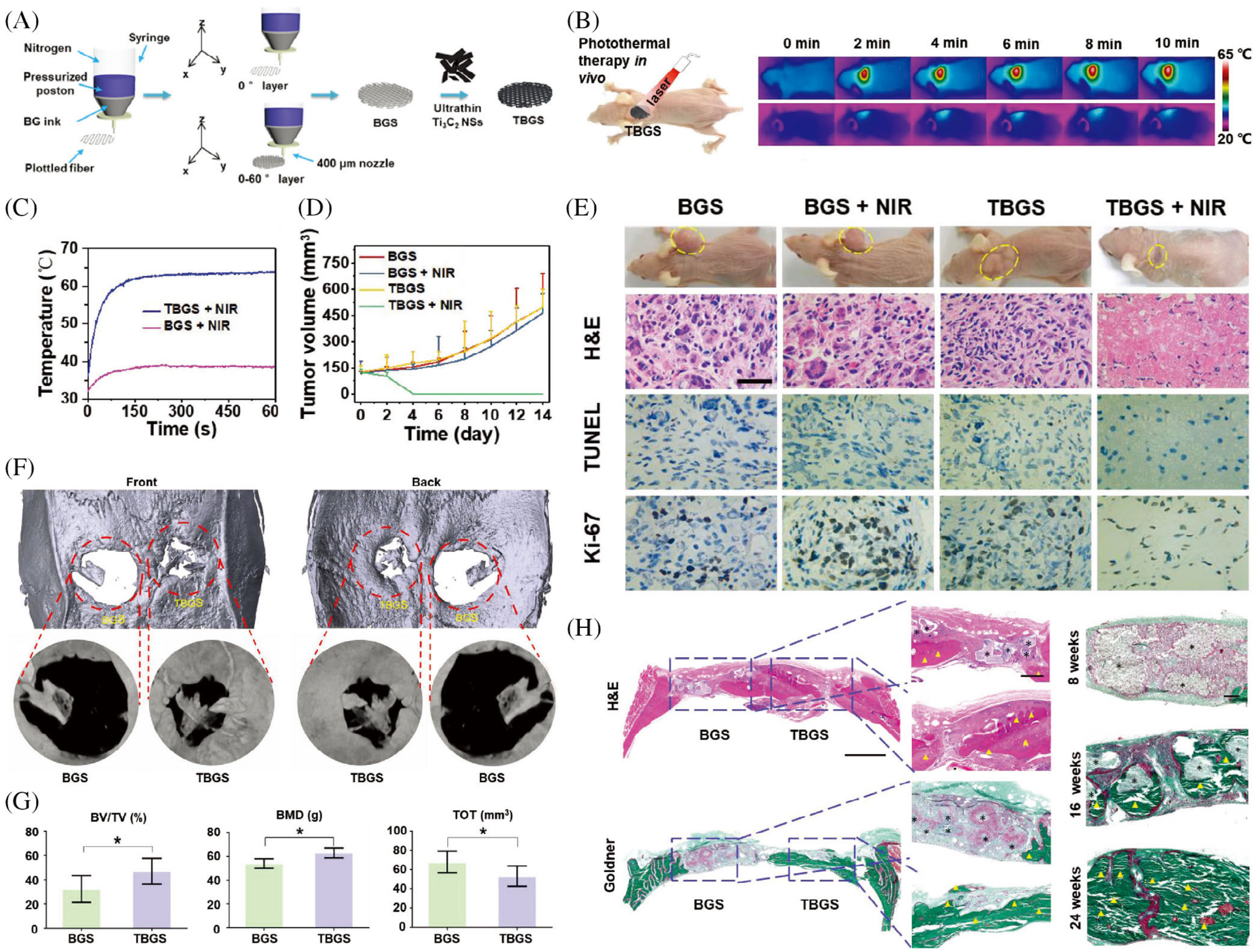

FIGURE 5 (A) The fabrication process of TBGS. (B) Schematic illustrating TBGSs for photothermal therapy and the corresponding in vivo thermal images in BGS + laser group (upper) and TBGS + laser group (bottom). (C) Temperature elevations at tumor sites of mice in different groups. (D) Time-dependent tumor-growth curves after different treatments. (E) Photographs of tumor-bearing mice on 14th day after different treatments, and the tumor tissues stained by H&E, TUNEL (apoptosis), and Ki-67 (proliferation) in 1 day after different treatments. (F) 3D reconstruction of circular defects at 24 weeks after scaffolds implantation. (G) Value of BV/TV, BMD, and TOT in newborn osseous tissue (**p* < .05, ***p* < .01, ****p* < .001); (H) Histology staining of craniums of rats implanted with BGS/TBGS at week 24. Implanted scaffolds that were not biodegraded completely (black asterisks). Newborn osseous tissue (yellow triangles). Adapted with permission from Reference 136.

periodontal ligament cells (PDLCs),[128] some scholars have researched the impact of $Ti_3C_2T_x$ MXene nanoflakes on PDLCs.[106] The application of $Ti_3C_2T_x$ MXene nanoflakes facilitated the osteogenic differentiation of PDLCs by up-regulating the expression of osteogenic related genes such as RUNX-2, ALP, and OPN. In the rats with periodontal fenestration defects model, $Ti_3C_2T_x$-treated hPDLCs inhibited osteoclastic activity and accelerated alveolar bone regeneration, which might be via regulating the metabolic reprogramming-related HIF-1α/WNT signaling pathway.[106]

3.2.3 | MXene nanomaterials as a scaffold

Three-dimensional biodegradable scaffold is the most common strategy in bone tissue engineering to restore the mechanical integrity of bone defects and provide space to simulate the natural process of bone reconstruction.[129] This scaffold can create an ideal microenvironment via imitating extracellular matrix, which can be adopted for the attachment, proliferation, migration and differentiation of osteoblasts and as the carrier of growth factors.[130] Owing to the outstanding mechanical and biological properties, more and more studies focus on using MXene as a scaffold or a reinforcement material in scaffold to repair large bone defects.

Bone cancers occur in the bone or originate from various bone tissue components, presenting as severe pain and pathological fractures.[131,132] Nowadays, the main and widely used mean to eliminate bone tumors is surgical resection, supplemented by radiotherapy and chemotherapy.[133–135] However, surgery has two main shortcomings that lead to failure: One is that the eradication of bone tumors is not complete and the risk of recurrence is high; The other is that surgical resection would cause large bone defects. The traditional therapy relies on the implantation orthopedic materials to pad the bone defect space, but it could not eliminate the residual tumor cells. Hence, it is fully essential to fabricate a treatment platform that can effectively clear up bone tumors and promote bone reconstruction at the same time. Pan et al. reported a 2D Ti_3C_2 MXene-integrated 3D-printing bioactive glass scaffold,[136] assembling photothermal properties and osteogenic potential of MXene nanomaterials (Figure 5A). With NIR laser irradiation, the latent malignant tumor cells were ablated at high temperature, and no cancer recurrence was observed in rats after 2 weeks (Figure 5B–E). Moreover, the addition of MXene, compared with a pure bioactive glass scaffold, markedly excited in vivo formation and growth of new bone (Figure 5F–H). In the process of bone tumor elimination and postoperative bone reconstruction, Ti_3C_2 MXene nanoflakes in the composite scaffold will gradually be biodegradable into Ti based species, thereby accelerating the formation of new bone. In one investigation, researchers assembled a novel multifunctional composite scaffold platform with controllable NO release and efficient photothermal conversion performance through modifying 2D Nb_2C MXene materials, which supplies an innovative way of synergistic gas therapy and photothermal therapy for eradicating residual tumor cells and repairing bone defect.[137] Specifically, the surface of Nb_2C MXene is coated with a mesoporous silica layer, which enables the NO donor S-nitrosothiol to be effectively loaded on the surface of MXene. On the one hand, the high photothermal conversion efficiency of 2D MXene and the release of high concentration NO can eliminate tumors. On the other hand, low concentration of NO in the later stage can promote bone regeneration. In addition, angiogenesis is pivotal link of bone development and growth.[138,139] Blood vessels transport essential nutrients, oxygen and BMSCs for bone regeneration in bone defect area after osteosarcoma resection. Several scholars noted that Nb_2C MXene in the 3D scaffolds observably accelerated the migration of human umbilical endothelial vein cells (HUVECs), facilitate the growth of honeycomb tube, and promote the expression of angiogenesis related genes.[140] When the scaffold integrated Nb_2C MXene was implanted into the animal model for 3 weeks, a dense new blood vessel network was displayed around the scaffold, which greatly promoted the growth of new bone. Furthermore, malignant tumor cells such as breast cancer cells and lung cancer cells are often transferred to bone tissue.[141,142] Compared with removing primary tumors, eliminating metastatic bone tumor is more challenging. Currently, Immunotherapy can eradicate metastatic tumors by awakening the systemic immune system.[143–145] He et al. herein designed a Nb_2C MXene nanosheets loaded with immune adjuvant (R837)and integrated them on BG scaffolds.[146] Studies has demonstrated that Nb_2C MXene can not only destroy tumors through photothermal effect, but also act as a drug delivery system to carry and release R837 which can drive dendritic cells to mature and active the immune responses of antitumor. Furthermore, Nb-based species form the Nb_2C MXene can facilitate bone regeneration and reconstruction. In the animal experiment, the density and volume fraction of new bone in the Nb_2C incorporated-scaffold group increased more than that in the control group.

3.3 | MXene nanomaterials for neural tissue engineering and regeneration

Owing to the complexity of nervous system, repairing and regenerating neural tissue is still a major challenge in clinical treatment.[147] The traditional approaches for repairing never injuries include microsurgical neurorrhaphy, autografts or allografts, nevertheless, these means still have several flaws such as surgical trauma and subsequent complications, immunological responses and donor site morbidity.[2] Neural tissue engineering is deemed as an ideal solution strategy for repairing and reconstructing injured neural tissue. Over the past few years, 2D nanomaterials containing MXene have broad application prospects in the field of neural tissue engineering and regeneration, attributing to their fascinating biocompatibility, biodegradability, especially conductivity.

Guo et al. evaluated the effect of $Ti_3C_2T_x$ MXene nanomaterials on neural stem cells (NSCs).[148] Their work confirmed that the MXene films was biocompatibility with NSCs. Growing on $Ti_3C_2T_x$ MXene substrates, the ability of the differentiation of NSCs into neurons was enhanced, which was manifested the increase of neuron percentage, length of longest neurites and numbers of branch points (Figure 6). Also, the MXene films coupled electrical stimulation could significantly enhance the expression of proliferation-associated genes PCNA and Ki67, thereby promoting the proliferation of NSCs. Several scientists have reported a particular graphene oxide-MXene (rGO-MXene) hydrogel with porous structure.[149] The existence of MXene endows the hydrogel with better hydrophilicity and stiffness. The cells represent superior adhesion and migration ability on the surface and can grow along the netlike path of rGO-MXene based hydrogel to form a cell network. In addition, NSCs cultured on MXene substrates emerged strong neural network activities such as synaptic transmission and vesicle delivery, addicting $Ti_3C_2T_x$ MXene nanomaterials could improve the functional activity of NSCs.[148] A study showed that neuros could adhere to the Ti_3C_2 MXene neural interface, subsequently grow axons and form corresponding neural networks.[150] Fu et al. fabricated a fiber with conductive $Ti_3C_2T_x$ MXene as sheath and alginate as core (MXene@A fibers).[151] Due to the high surface area, rich functional groups, and hydrophilic property of MXene, the composite MXene@A fibers can act as a bio-interface to adsorb plenty of poly-L-lysine and protein via hydrogen bonding, thus offering a proper microenvironment for guiding the attachment, differentiation and directional migration of neural steam/progenitor cells. Further detection observe that MXene@A fibers drive the functional maturation of neurons through accelerating the formation and growth of synapses. Understanding the basic mechanism of neural circuit and how neural activities change in disease or injury is conducive to further explore the causes of nervous system diseases and develop relevant therapy methods.[152] According to the ultrathin conductive Ti_3C_2 MXene micropatterns, researchers simply and efficiently fabricated a field-effect transistor for detecting dopamine sensitively and monitoring the peak activities of hippocampal neurons.[153] Besides, high-resolution neural interfaces are also crucial tools for researching and regulating neural circuits. With splendid electrical properties and high specific surface area, Ti_3C_2 MXene has become a promising neural interface material for recording brain signals.

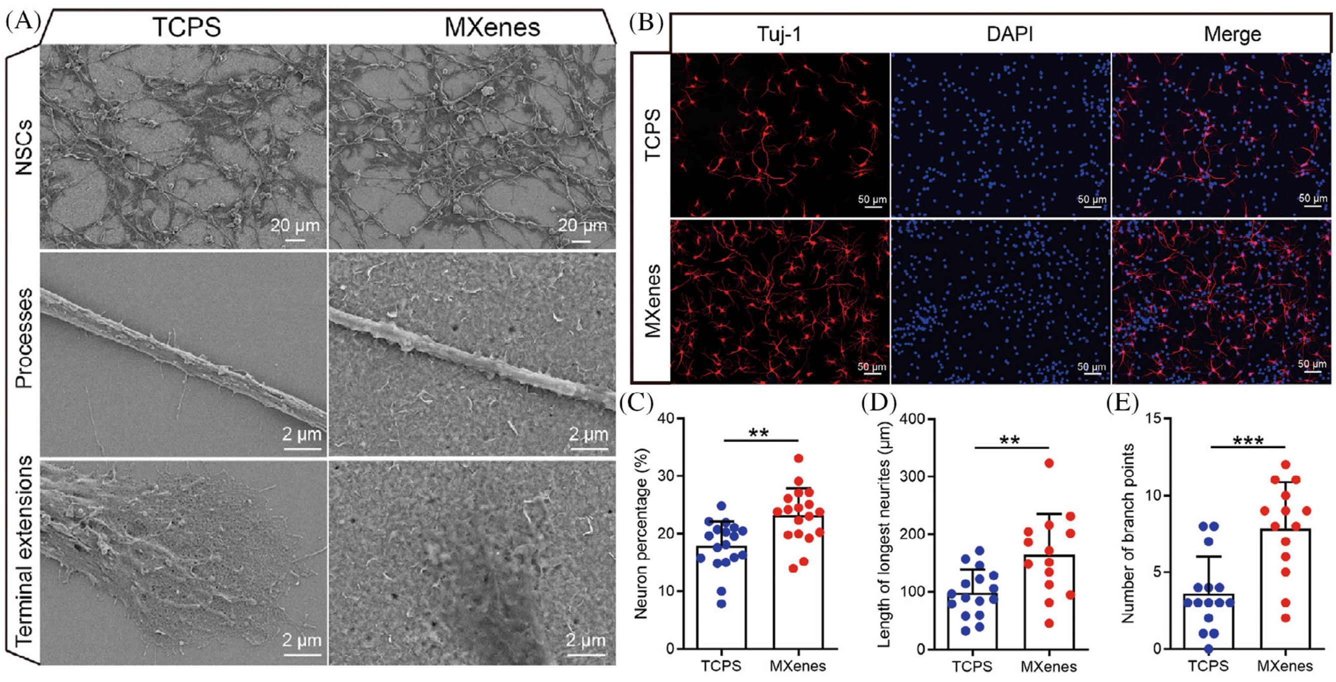

FIGURE 6 (A) Representative field-emission scanning electron microscopy images of NSCs cultured on TCPS and $Ti_3C_2T_x$ MXene film. (B) Representative fluorescent images of NSC progeny cultured on $Ti_3C_2T_x$ MXene film and TCPS substrate after NSCs were induced to differentiate for 7 days. βIII-tubulin (red), and nuclei (blue). (C–E) Histograms of the neuron percentage (C), the length of the longest neurites (D), the number of branch points (E). Adapted with permission from Reference 148.

3.4 | MXene nanomaterials for cardiac tissue engineering and regeneration

At present, cardiovascular disease is still one of the leading causes of death in the whole world.[154,155] The loss of myocardial blood supply caused by myocardial infarction (MI) leads to the injury and necrosis of heart tissue. Most of the damaged or necrotic cardiac tissue areas will be gradually replaced by fibrotic scar tissue, which would change the electrophysiological and systolic function of the myocardial field, and may eventually lead to fatal arrhythmia.[156] Heart transplantation is the ultimate solution to late MI. However, due to the lack of cardiac donors and the complications related to immunosuppressive therapy, scientists and surgeons have been looking for new strategies to treat the damaged heart.[157,158] The presence of cardiac tissue engineering may play a crucial role in replacing and maintaining the function of infarcted myocardial tissue and saving the lives of patients.[159,160]

Given that the heart needs electrical synaptic interaction between cells to perform physiological function, the biomedical materials used for cardiac tissue engineering must support bioelectric signal conduction and mediate communication between cardiomyocytes (CMs) to realize the synchronous beating of the heart.[8] As a burgeoning 2D nanomaterial with attractive electrical conductivity, hydrophilicity and biocompatibility, MXene is an ideal candidate for cardiac tissue engineering. In one investigation, through the technology of aerosol jet printing, the authors assembled a composite material composed of $Ti_3C_2T_x$ MXene nanoflakes and polyethylene glycol (PEG) hydrogels as an engineering human cardiac patch. The integration of MXene gives the hydrogel excellent conductivity, which is conducive to improving the synchronous beating of human induced pluripotent stem cell derived cardiomyocytes (iCMs) and the electrophysiological coupling between the patch and the infarcted area.[161] This composite also realistically imitated the structural arrangement and electrophysiological characteristics of cardiomyocytes in natural heart tissue, and promoted the maturation of ICMs. In another study, researchers prepared a novel engineering human cardiac muscle patch by introducing Ti_2C MXene nanoparticles into cryogel (Figure 7A).[162] When cardiomyocytes were cultured in Ti_2C-cryogel for 7 days, clear Z-line structures and packed strong sarcomeres and desmosomes which are key signs of myocardial maturation were observed under transmission electron microscopy (TEM) (Figure 7B). Remarkably, it was found that the infarct area was reduced (Figure 7C,D), the inflammatory response was weakened, the immunological microenvironment conducive to myocardial tissue repair was established, the dense micro-vessels were formed, and the myocardial function was distinctly improved when the heart patch was implanted into the rat model with MI for 4 weeks.[162]

4 | FUTURE TRENDS OF MXENE IN TISSUE ENGINEERING AND REGENERATION

MXene have been listed above as excellent nanomaterials in various tissue engineering fields. Currently, with the continuous optimization and development of manufacturing technology and nanotechnology,

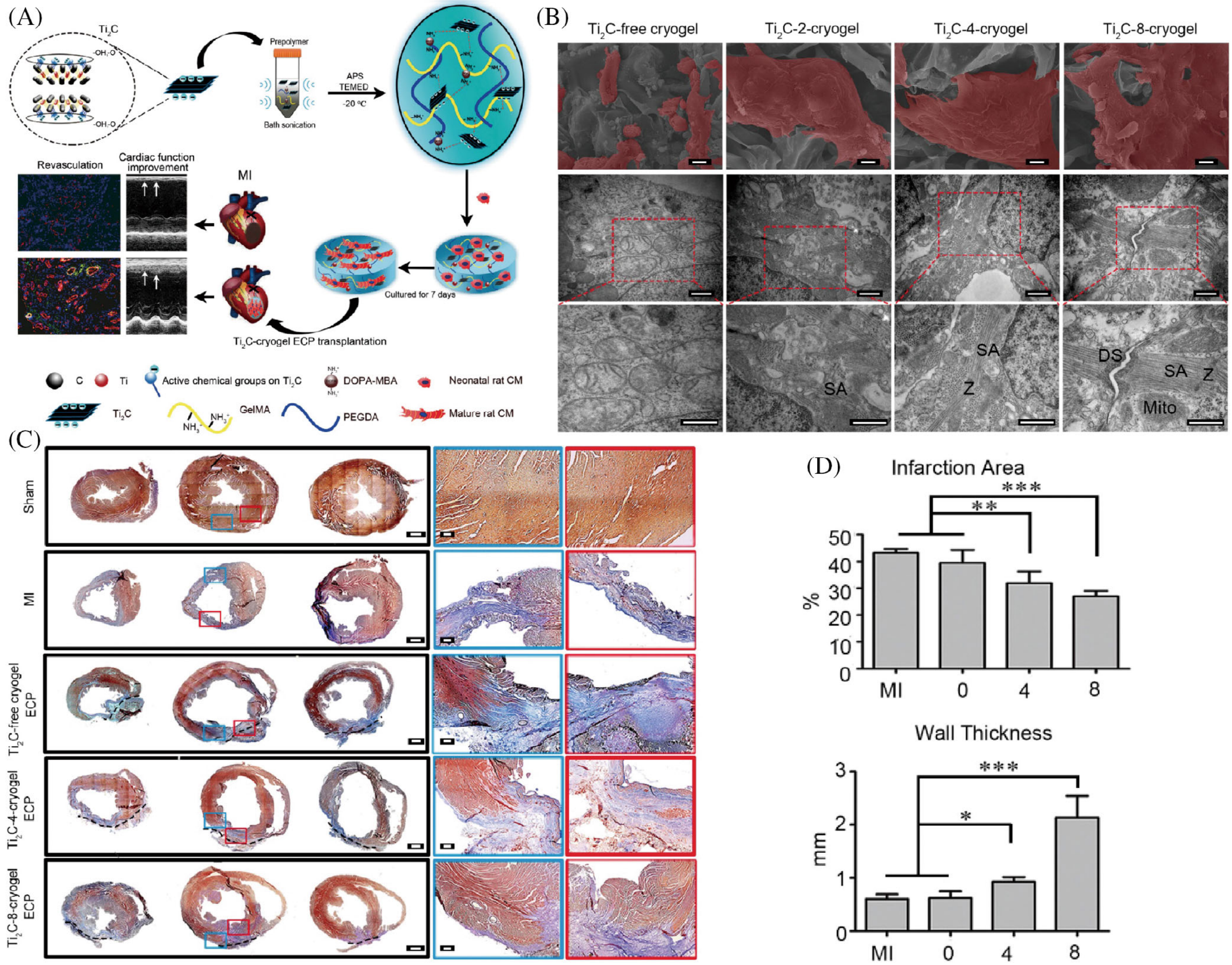

FIGURE 7 (A) Schematic illustration of the formation of Ti_2C-cryogel and its application in a rat MI model. (B) Ultrastructure of the CMs cultured on the different groups on day 7 of culture. Sarcomeres (SA), Z-lines (Z), mitochondria (Mito) and desmosomes (DS). (C) Masson's trichrome staining for multiple heart sections in different groups (fibrous tissue [blue] and myocardium [red]). (D) Quantitative analysis of wall thickness and infarct area of left ventricular anterior wall based on the images of Masson's trichrome staining. (**p* < .05, ***p* < .01, ****p* < .001). Adapted with permission from Reference 162.

the application of some new types of MXene nanomaterials in tissue engineering and regeneration is also worthy of our expectation.

In particular, the invention of ultra-small size MXene quantum dots (MQDs) enriches the application of MXene nanomaterials in biomedical field such as bioimaging,[163,164] biosensing[165] and tumor therapy.[166] However, few studies have noticed on the application of MQDs in tissue engineering. Ti_3C_2 MQDs are endowed with salient immunomodulatory performance.[167] It was found that MQDs could inhibit the proliferation of various pro-inflammatory immune cells and further hinder the recruitment of immune cells into the damaged area.[168] Moreover, MQDs have good biocompatibility with BMSCs and induced pluripotent stem cell-derived fibroblasts. The above evidence suggests that MQDs can be used as a new immunomodulatory platform to improve the immune tolerance of transplanted cells, facilitate the survival and proliferation of stem cells, decreased the inflammatory responses and promote the remodeling after tissue injury. As we all know, the immune responses of grafts directly affect the effect of tissue regeneration. Excessive foreign body reaction would prolong the time of tissue healing, increase the formation of scar tissue. In the process of bone defect repair, the final osteogenic effect of bone substitute materials was influenced by bone immune microenvironment. Thus, future study can combine MQDs with existing biomaterials to explore new application prospects of MXene in tissue engineering from the perspective of immunomodulation.

By combining 3D printing technology with tissue engineering technology, 3D bioprinting technology can take biomaterials and/or cells as printing materials and print out in vitro 3D biological functional objects with complex physiological structure and function according to the requirements of bionic morphology, biological function and cell microenvironment to repair and reconstruct bone, cartilage, blood vessels and nerve tissues.[7,112,169] Bioinks, as the material of biological 3D printing technology, play a vital role in this process. Ideal bioinks need to have good bioactivity and formability. Rastin's group first introduced MXene nanosheets into 3D bioprinting as a raw material of bioinks.[170] They prepared a new class of electro-conductive bioinks by evenly dispersed Ti_3C_2 MXene nanosheets in hyaluronic acid/alginate hydrogel. It is found that the complex 3D structure printed with the composite bioinks has higher shape fidelity and resolution. Besides, MXene nanosheets also gives the ink higher conductivity, making it more compatible with the physicochemical characteristics of the tissue. The results of cell experiment illustrated that the encapsulated Human Embryonic Kidney 293 (HEK-293) cells showed high cell viability (>95%) in the 3D bioprinting structure, indicating that MXene nanocomposite bioinks had excellent biocompatibility.[170] Therefore, MXene nanocomposite bioinks with splendid biocompatibility, biodegradability and electrical conductivity is an optimal choice in 3D printing technology and can expand some new application modes in neural engineering.

Furthermore, due to the particular layered structure, hydrophilic properties, and plentiful terminal groups on the surface of MXene nanomaterials, water, organic molecules, and metal cations thus can be easily inserted into the layered structure of MXene nanomaterials, making it a potential adsorbent.[171–174] At present, MXene nanosheets have been reported as adsorbents for the regeneration of dialysate. Meng et al. noted that when the initial concentration of urea was 30 mg/dl, the removal rate of urea in aqueous solution and dialysate by $Ti_3C_2T_x$ MXene as adsorbent separately reached 99% and 94% respectively. At 37°C, the maximum urea adsorption ability of MXene nanosheets is 21.7 mg/g.[175] In another study, the researchers found that the maximum adsorption ability of $Ti_3C_2T_x$ MXene nanomaterial for creatinine and uric acid from aqueous solution and dialysate reached 45.7 and 17.0 mg/g, respectively.[176] Compared with the traditional activated carbon adsorbent, the interlayer structure and hydrophilic end of MXene material have higher adsorption density, so as to reduce the use of dialysate, which is undoubtedly a great gospel for patients with end-stage renal disease. Even so, further surface modification may give MXene nanomaterials stronger adsorption capacity, which needs special consideration in future study.

5 | CONCLUSIONS AND CHALLENGES

Focusing on MXene, a rookie in the 2D nanomaterial family, this review summarizes its preparation and surface modification methods, then respectively emphasizes its application in skin, bone, neural and cardiac tissue engineering, and finally briefly introduces the emerging research trend of MXene in the field of tissue engineering and regeneration. As we all know, stem cells, supporting materials and growth factors are the three key elements of tissue engineering. Thanks to the unique physicochemical and biological properties of MXene nanomaterials, they have great application potential in tissue regeneration (Figure 8).

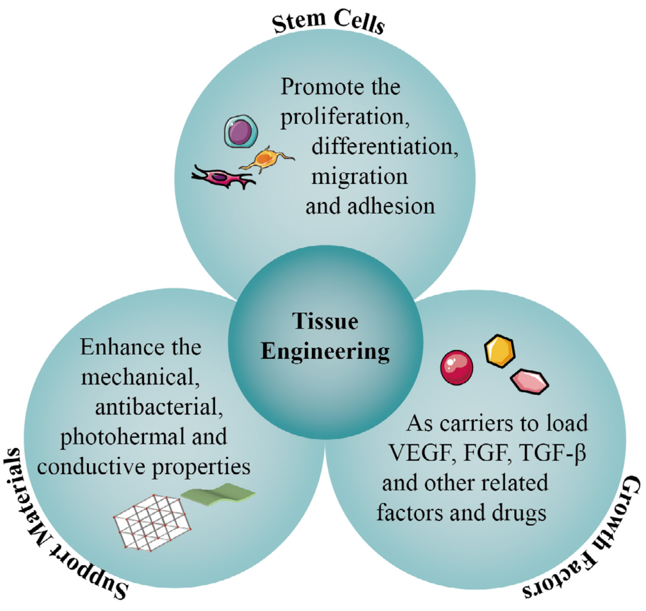

FIGURE 8 The role of MXene nanomaterials in tissue engineering analyzed from three aspects.

MXene can promote the proliferation, differentiation, adhesion and migration of a variety of tissue engineering stem cells without obvious cytotoxicity; Its excellent antibacterial properties make it eliminate bacteria and conducive to the healing of infected wounds and prevent the occurrence of peri-implant infections; MXene is endowed with high specific surface area and conductivity, which provides favorable conditions for the interaction and transmission of bioelectric signals between cells, making it possible for the synchronous beating of repaired heart tissue and the functional integrity of regenerated neural tissue; Moreover, the superior photothermal and photodynamic properties make MXene nanomaterials not only ablate tumor cells, but also facilitate the proliferation of related cells. For example, it has enormous potential in the repair of bone defects after bone cancer resection. In view of splendid hydrophilicity, biodegradability and biocompatibility of MXene, it is a potential component of tissue engineering scaffolds, membranes and coatings. First of all, MXene can form a scaffold composite with hydrogel or bioactive glass, simulate the extracellular matrix environment, induce stereotaxic growth of cells, reduce inflammation and promote angiogenesis. Second, the bioactive barrier prepared by MXene as GBR membrane can prevent the infiltration of surrounding soft tissue into the bone defect area and accelerate the reconstruction of bone tissue on the side of bone defect. When the damaged tissue is repaired, the MXene-based scaffold and membrane are also absorbed by biodegradation. As a coating, the implant surface wrapped by MXene significantly promotes the osseointegration ability of the implant and makes it more stable and firmer. In addition, strong antibacterial performance would be presented when the wound dressing is covered with a layer of $Ti_3C_2T_x$. At present, scaffold complex, membrane and coating made of MXene have been well used in hard and soft tissue engineering. MXene surface has rich functional groups, which can be modified flexibly. Attaching growth factors such as TGF-β and FGF to the surface of MXene nanosheets can regulate the growth and differentiation of seed cells. Certainly, the surface of MXene nanomaterials can also be modified to load some drugs to strengthen its antibacterial, anti-inflammatory and tissue repair effects.

Although MXene and MXene-based nanomaterials have made many brilliant scientific research achievements in the application of tissue engineering in the past years, the present study still focuses on the repair and remodeling of skin and bone tissue, and pays less attention to neural and cardiac tissue engineering. Moreover, most studies are still in the initial stage of laboratory exploration, so there still exist several problems needed to resolved before MXene nanomaterials enter clinical and practical application. (1) The content, size, thickness and morphology of MXene have a crucial impact on the overall properties of biomaterials. The effects of MXene nanomaterials with specific structure on different tissues and cells need to be further studied, which will contribute to better apply MXene to strengthen the function of composite materials to promote tissue repair and regeneration. (2) At present, we know little about the potential mechanisms and signal transduction pathways related to cell proliferation and differentiation involved in MXene. Further understanding and exploring these molecular mechanisms can open up a new way for the development of MXene-based scaffolds and GBR membranes for tissue engineering. (3) The biosafety research of MXene materials cannot be ignored. Although most studies show that MXene is endowed with good biocompatibility and degradability, there is still a lack of systematic analysis and evaluation of the long-term biosafety of MXene nanomaterial and its degradation products. In the future, researchers need to make a lot of efforts to understand the long-term toxicity, immunogenicity, pharmacokinetics and biological distribution of MXene nanomaterials in animal models. (4) How to make rational use of various excellent properties of MXene in tissue engineering to produce synergistic effects to accelerate the repair and reconstruction of injured tissues also needs further research and exploration. A comprehensive assessment of in vivo repair and regeneration performance, corresponding mechanism and time dependence of MXene and MXene-based composites can provide a basis for its future improvement and clinical application. (5) Safe and large-scale production is a key step to realize the clinical application of MXene. Currently, the fabrication of MXene nanomaterials by fluorine-containing technology is relatively dangerous and inefficient. It is particularly necessary to develop safer, more efficient, simpler and more environmentally friendly low fluorine or fluorine-free preparation methods and find more stable surface modification technologies. Moreover, under high temperature or oxygen-containing environment, MXene has poor stability and is easy to be oxidized, and its performance will change accordingly. Therefore, how to prevent MXene oxidation in the process of production and storage is particularly significant. It is believed that with the development of manufacturing technology and biomaterial science and the unremitting efforts of scientists, MXene nanomaterials will give full play to its unique advantages in the field of tissue engineering and regeneration.

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

REFERENCES

1. Jiang C, Wang K, Liu Y, Zhang C, Wang B. Application of textile technology in tissue engineering: a review. *Acta Biomater*. 2021;128:60-76.
2. Halim A, Qu KY, Zhang XF, Huang NP. Recent advances in the application of two-dimensional nanomaterials for neural tissue engineering and regeneration. *ACS Biomater Sci Eng*. 2021;7(8):3503-3529.
3. Cheng J, Liu J, Wu B, et al. Graphene and its derivatives for bone tissue engineering: in vitro and in vivo evaluation of graphene-based scaffolds. *Membr Coat Front Bioeng Biotechnol*. 2021;9:734688.
4. Goldenberg D, McLaughlin C, Koduru SV, Ravnic DJ. Regenerative engineering: current applications and future perspectives. *Front Surg*. 2021;8:731031.
5. Langer R, Vacanti J. Advances in tissue engineering. *J Pediatr Surg*. 2016;51(1):8-12.
6. Oprea M, Voicu SI. Cellulose composites with graphene for tissue engineering applications. *Materials (Basel)*. 2020;13(23):5347.
7. Saini G, Segaran N, Mayer JL, Saini A, Albadawi H, Oklu R. Applications of 3D bioprinting in tissue engineering and regenerative medicine. *J Clin Med*. 2021;10(21):4966.
8. Rogers ZJ, Zeevi MP, Koppes R, Bencherif SA. Electroconductive hydrogels for tissue engineering: current status and future perspectives. *Bioelectricity*. 2020;2(3):279-292.
9. Guazzo R, Gardin C, Bellin G, et al. Graphene-based nanomaterials for tissue engineering in the dental field. *Nanomaterials*. 2018;8(5):349.
10. Liu Y, Yu Q, Chang J, Wu C. Nanobiomaterials: from 0D to 3D for tumor therapy and tissue regeneration. *Nanoscale*. 2019;11(29):13678-13708.
11. Lalwani G, Patel SC, Sitharaman B. Two- and three-dimensional all-carbon nanomaterial assemblies for tissue engineering and regenerative medicine. *Ann Biomed Eng*. 2016;44(6):2020-2035.
12. Gokce C, Gurcan C, Delogu LG, Yilmazer A. 2D materials for cardiac tissue repair and regeneration. *Front Cardiovasc Med*. 2022;9:802551.
13. Zhang JY, Chen HL, Zhao M, Liu GT, Wu J. 2D nanomaterials for tissue engineering application. *Nano Res*. 2020;13(8):2019-2034.
14. Naguib M, Mashtalir O, Carle J, et al. Two-dimensional transition metal carbides. *ACS Nano*. 2012;6(2):1322-1331.
15. Naguib M, Mochalin VN, Barsoum MW, Gogotsi Y. 25th anniversary article: MXenes: a new family of two-dimensional materials. *Adv Mater*. 2014;26(7):992-1005.
16. Soleymaniha M, Shahbazi MA, Rafieerad AR, Maleki A, Amiri A. Promoting role of MXene nanosheets in biomedical sciences: therapeutic and biosensing innovations. *Adv Healthc Mater*. 2019;8(1):e1801137.
17. Huang H, Feng W, Chen Y. Two-dimensional biomaterials: material science, biological effect and biomedical engineering applications. *Chem Soc Rev*. 2021;50(20):11381-11485.
18. Pang J, Mendes RG, Bachmatiuk A, et al. Applications of 2D MXenes in energy conversion and storage systems. *Chem Soc Rev*. 2019;48(1):72-133.
19. Aierken Y, Sevik C, Gulseren O, Peeters FM, Cakir D. MXenes/graphene heterostructures for Li battery applications: a first principles study. *J Mater Chem A*. 2018;6(5):2337-2345.

20. Rasool K, Pandey RP, Rasheed PA, Buczek S, Gogotsi Y, Mahmoud KA. Water treatment and environmental remediation applications of two-dimensional metal carbides (MXenes). *Mater Today*. 2019;30:80-102.
21. Lu B, Zhu Z, Ma B, Wang W, Zhu R, Zhang J. 2D MXene nanomaterials for versatile biomedical applications: current trends and future prospects. *Small*. 2021;17(46):e2100946.
22. Sundaram A, Ponraj JS, Wang C, et al. Engineering of 2D transition metal carbides and nitrides MXenes for cancer therapeutics and diagnostics. *J Mater Chem B*. 2020;8(23):4990-5013.
23. Fu B, Sun J, Wang C, et al. MXenes: synthesis, optical properties, and applications in ultrafast photonics. *Small*. 2021;17(11):e2006054.
24. Sun Y, Li Y. Potential environmental applications of MXenes: a critical review. *Chemosphere*. 2021;271:129578.
25. Iravani S, Varma RS. MXenes and MXene-based materials for tissue engineering and regenerative medicine: recent advances. *Mater Adv*. 2021;2(9):2906-2917.
26. Huang H, Dong CH, Feng W, Wang Y, Huang BC, Chen Y. Biomedical engineering of two-dimensional MXenes. *Adv Drug Deliv Rev*. 2022;184:114178.
27. Xu C, Wang L, Liu Z, et al. Large-area high-quality 2D ultrathin Mo2C superconducting crystals. *Nat Mater*. 2015;14(11):1135-1141.
28. Li T, Yao L, Liu Q, et al. Fluorine-free synthesis of high-purity Ti(3) C (2) T(x) (T=OH, O) via alkali treatment. *Angew Chem Int Ed Engl*. 2018;57(21):6115-6119.
29. Sun W, Shah SA, Chen Y, et al. Electrochemical etching of Ti2AlC to Ti2CTx (MXene) in low-concentration hydrochloric acid solution. *J Mater Chem A*. 2017;5(41):21663-21668.
30. Urbankowski P, Anasori B, Makaryan T, et al. Synthesis of two-dimensional titanium nitride Ti4N3 (MXene). *Nanoscale*. 2016;8(22):11385-11391.
31. Lin X, Li Z, Qiu J, et al. Fascinating MXene nanomaterials: emerging opportunities in the biomedical field. *Biomater Sci*. 2021;9(16):5437-5471.
32. Iravani S, Varma RS. MXenes for cancer therapy and diagnosis: recent advances and current challenges. *ACS Biomater Sci Eng*. 2021;7(6):1900-1913.
33. Zamhuri A, Lim GP, Ma NL, Tee KS, Soon CF. MXene in the lens of biomedical engineering: synthesis, applications and future outlook. *Biomed Eng Online*. 2021;20(1):33.
34. Zhang C, Ma YL, Zhang XT, et al. Two-dimensional transition metal carbides and nitrides (MXenes): synthesis, properties, and electrochemical energy storage applications. *Energy Environ Mater*. 2020;3(1):29-55.
35. Naguib M, Kurtoglu M, Presser V, et al. Two-dimensional nanocrystals produced by exfoliation of Ti3 AlC2. *Adv Mater*. 2011;23(37):4248-4253.
36. Ghidiu M, Lukatskaya MR, Zhao MQ, Gogotsi Y, Barsoum MW. Conductive two-dimensional titanium carbide 'clay' with high volumetric capacitance. *Nature*. 2014;516(7529):78-81.
37. Halim J, Lukatskaya MR, Cook KM, et al. Transparent conductive two-dimensional titanium carbide epitaxial thin films. *Chem Mater*. 2014;26(7):2374-2381.
38. Li M, Lu J, Luo K, et al. Element replacement approach by reaction with Lewis acidic molten salts to synthesize nanolaminated MAX phases and MXenes. *J Am Chem Soc*. 2019;141(11):4730-4737.
39. Yu X, Cai X, Cui H, Lee SW, Yu XF, Liu B. Fluorine-free preparation of titanium carbide MXene quantum dots with high near-infrared photothermal performances for cancer therapy. *Nanoscale*. 2017;9(45):17859-17864.
40. Joshi S, Wang Q, Puntambekar A, Chakrapani V. Facile synthesis of large area two-dimensional layers of transition-metal nitride and their use as insertion electrodes. *ACS Energy Letters*. 2017;2(6):1257-1262.
41. Zhang F, Zhang Z, Wang HC, et al. Plasma-enhanced pulsed-laser deposition of single-crystalline Mo2C ultrathin superconducting films. *Phys Rev Mater*. 2017;1(3):034002.
42. Zhang Z, Zhang F, Wang HC, Chan CH, Lu W, Dai JY. Substrate orientation-induced epitaxial growth of face centered cubic Mo2C superconductive thin film. *J Mater Chem C*. 2017;5(41):10822-10827.
43. Lin H, Chen Y, Shi J. Insights into 2D MXenes for versatile biomedical applications: current advances and challenges ahead. *Adv Sci (Weinh)*. 2018;5(10):1800518.
44. Verger L, Xu C, Natu V, Cheng HM, Ren WC, Barsoum MW. Overview of the synthesis of MXenes and other ultrathin 2D transition metal carbides and nitrides. *Curr Opin Solid State Mater Sci*. 2019;23(3):149-163.
45. Lin H, Wang X, Yu L, Chen Y, Shi J. Two-dimensional ultrathin MXene ceramic nanosheets for photothermal conversion. *Nano Lett*. 2017;17(1):384-391.
46. Xuan J, Wang Z, Chen Y, et al. Organic-base-driven intercalation and delamination for the production of functionalized titanium carbide nanosheets with superior photothermal therapeutic performance. *Angew Chem Int Ed Engl*. 2016;55(47):14569-14574.
47. Zhang P, Yang XJ, Li P, Zhao Y, Niu QJ. Fabrication of novel MXene (Ti(3)C(2))/polyacrylamide nanocomposite hydrogels with enhanced mechanical and drug release properties. *Soft Matter*. 2020;16(1):162-169.
48. Zhu X, Liu B, Hou H, et al. Alkaline intercalation of Ti3C2 MXene for simultaneous electrochemical detection of cd(II), Pb(II), cu(II) and hg(II). *Electrochim Acta*. 2017;248:46-57.
49. Hu Y, Chu H, Ma X, Li Y, Zhao S, Li D. Enhanced optical nonlinearities in Ti3C2 MXene decorated Fe3O4 nanocomposites for highly stable ultrafast pulse generation. Materials today. *Phys Ther*. 2021;21:100482.
50. Tang W, Dong Z, Zhang R, et al. Multifunctional two-dimensional core-shell MXene@gold nanocomposites for enhanced photo-radio combined therapy in the second biological window. *ACS Nano*. 2019;13(1):284-294.
51. Dai C, Chen Y, Jing X, et al. Two-dimensional tantalum carbide (MXenes) composite nanosheets for multiple imaging-guided photothermal tumor ablation. *ACS Nano*. 2017;11(12):12696-12712.
52. Liu Y, Han Q, Yang W, et al. Two-dimensional MXene/cobalt nanowire heterojunction for controlled drug delivery and chemo-photothermal therapy. *Mater Sci Eng C Mater Biol Appl*. 2020;116:111212.
53. Tu X, Gao F, Ma X, et al. Mxene/carbon nanohorn/β-cyclodextrin-metal-organic frameworks as high-performance electrochemical sensing platform for sensitive detection of carbendazim pesticide. *J Hazard Mater*. 2020;396:122776.
54. Lin H, Wang Y, Gao S, Chen Y, Shi J. Theranostic 2D tantalum carbide (MXene). *Adv Mater*. 2018;30(4):1703284.
55. Liu Z, Lin H, Zhao M, et al. 2D superparamagnetic tantalum carbide composite MXenes for efficient breast-cancer theranostics. *Theranostics*. 2018;8(6):1648-1664.
56. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: an update on the current knowledge and concepts. *Eur Surg Res*. 2017;58(1–2):81-94.
57. Takeo M, Lee W, Ito M. Wound healing and skin regeneration. *Cold Spring Harb Perspect Med*. 2015;5(1):a023267.
58. Johnson TR, Gómez BI, McIntyre MK, et al. The cutaneous microbiome and wounds: new molecular targets to promote wound healing. *Int J Mol Sci*. 2018;19(9):2699.
59. Caldwell MD. Bacteria and antibiotics in wound healing. *Surg Clin North Am*. 2020;100(4):757-776.

60. Rasool K, Helal M, Ali A, Ren CE, Gogotsi Y, Mahmoud KA. Antibacterial activity of Ti_3C_2Tx MXene. *ACS Nano*. 2016;10(3):3674-3684.
61. Shamsabadi AA, Gh MS, Anasori B, Soroush M. Antimicrobial mode-of-action of colloidal Ti3C2TX MXene nanosheets. *ACS Sustain Chem Eng*. 2018;6(12):16586-16596.
62. Rozmysłowska-Wojciechowska A, Karwowska E, Gloc M, et al. Controlling the porosity and biocidal properties of the chitosan-hyaluronate matrix hydrogel nanocomposites by the addition of 2D Ti(3)C(2)T(x) MXene. *Materials (Basel)*. 2020;13(20):4587.
63. Mayerberger EA, Street RM, McDaniel RM, Barsoum MW, Schauer CL. Antibacterial properties of electrospun Ti3C2Tz (MXene)/chitosan nanofibers. *RSC Adv*. 2018;8(62):35386-35394.
64. Zhou L, Zheng H, Liu Z, et al. Conductive antibacterial hemostatic multifunctional scaffolds based on Ti(3)C(2)T(x) MXene nanosheets for promoting multidrug-resistant bacteria-infected wound healing. *ACS Nano*. 2021;15(2):2468-2480.
65. Jastrzebska AM, Karwowska E, Wojciechowski T, et al. The atomic structure of Ti2C and Ti3C2 MXenes is responsible for their antibacterial activity toward *E. coli* bacteria. *J Mater Eng Perform*. 2019; 28(3):1272-1277.
66. Nesi-Reis V, Lera-Nonose D, Oyama J, et al. Contribution of photodynamic therapy in wound healing: a systematic review. *Photodiagnosis Photodyn Ther*. 2018;21:294-305.
67. Shanmugapriya K, Kang HW. Engineering pharmaceutical nanocarriers for photodynamic therapy on wound healing: review. *Mater Sci Eng C Mater Biol Appl*. 2019;105:110110.
68. Percival SL, Suleman L, Francolini I, Donelli G. The effectiveness of photodynamic therapy on planktonic cells and biofilms and its role in wound healing. *Future Microbiol*. 2014;9(9):1083-1094.
69. Yang Z, Fu X, Ma D, et al. Growth factor-decorated Ti(3) C(2) MXene/MoS(2) 2D bio-heterojunctions with quad-channel photonic disinfection for effective regeneration of bacteria-invaded cutaneous tissue. *Small*. 2021;17(50):e2103993.
70. Zhang S, Ye J, Liu X, et al. Titanium carbide/zeolite imidazole framework-8/polylactic acid electrospun membrane for near-infrared regulated photothermal/photodynamic therapy of drug-resistant bacterial infections. *J Colloid Interface Sci*. 2021;599: 390-403.
71. Ren X, Huo M, Wang M, et al. Highly catalytic niobium carbide (MXene) promotes hematopoietic recovery after radiation by free radical scavenging. *ACS Nano*. 2019;13(6):6438-6454.
72. Zhang X, Tan B, Wu Y, Zhang M, Liao J. A review on hydrogels with photothermal effect in wound healing and bone tissue engineering. *Polymers*. 2021;13(13):2100.
73. Zhu X, Zhu Y, Jia K, et al. A near-infrared light-mediated antimicrobial based on ag/Ti(3)C(2)T(x) for effective synergetic antibacterial applications. *Nanoscale*. 2020;12(37):19129-19141.
74. Xu X, Wang S, Wu H, Liu Y, Xu F, Zhao J. A multimodal antimicrobial platform based on MXene for treatment of wound infection. *Colloids Surf B Biointerfaces*. 2021;207:111979.
75. Li Y, Han MM, Cai Y, et al. Muscle-inspired MXene/PVA hydrogel with high toughness and photothermal therapy for promoting bacteria-infected wound healing. *Biomater Sci*. 2022;10(4):1068-1082.
76. Zhao X, Wang LY, Tang CY, et al. Smart Ti(3)C(2)T(x) MXene fabric with fast humidity response and joule heating for healthcare and medical therapy applications. *ACS Nano*. 2020;14(7):8793-8805.
77. Jin L, Guo XQ, Gao D, et al. NIR-responsive MXene nanobelts for wound healing. *NPG Asia Mater*. 2021;13(1):1-9.
78. Yang X, Zhang CQ, Deng DW, Gu YQ, Wang H, Zhong QF. Multiple stimuli-responsive MXene-based hydrogel as intelligent drug delivery carriers for deep chronic wound healing. *Small*. 2022;18(5):2104368.
79. Barnum L, Samandari M, Schmidt TA, Tamayol A. Microneedle arrays for the treatment of chronic wounds. *Expert Opin Drug Deliv*. 2020; 17(12):1767-1780.
80. Iriarte C, Awosika O, Rengifo-Pardo M, Ehrlich A. Review of applications of microneedling in dermatology. *Clin Cosmet Investig Dermatol*. 2017;10:289-298.
81. Sun L, Fan L, Bian F, Chen G, Wang Y, Zhao Y. MXene-integrated microneedle patches with innate molecule encapsulation for wound healing. *Research*. 2021;2021:9838490-9.
82. Luo R, Dai J, Zhang J, Li Z. Accelerated skin wound healing by electrical stimulation. *Adv Healthc Mater*. 2021;10(16):e2100557.
83. Ud-Din S, Bayat A. Electrical stimulation and cutaneous wound healing: a review of clinical evidence. *Healthcare*. 2014;2(4):445-467.
84. Cheah YJ, Buyong MR, Mohd Yunus MH. Wound healing with electrical stimulation technologies. *Rev Polym*. 2021;13(21):3790.
85. Mao L, Hu S, Gao Y, et al. Biodegradable and electroactive regenerated bacterial cellulose/MXene (Ti(3) C(2) T(x)) composite hydrogel as wound dressing for accelerating skin wound healing under electrical stimulation. *Adv Healthc Mater*. 2020;9(19):e2000872.
86. Guo M, Wang Y, Gao B, He B. Shark tooth-inspired microneedle dressing for intelligent wound management. *ACS Nano*. 2021;15(9): 15316-15327.
87. Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. *BMC Med*. 2011;9:66.
88. Katagiri W, Watanabe J, Toyama N, Osugi M, Sakaguchi K, Hibi H. Clinical study of bone regeneration by conditioned medium from mesenchymal stem cells after maxillary sinus floor elevation. *Implant Dent*. 2017;26(4):607-612.
89. Majidinia M, Sadeghpour A, Yousefi B. The roles of signaling pathways in bone repair and regeneration. *J Cell Physiol*. 2018;233(4): 2937-2948.
90. Zhang N, Zhang S, Xu C, Fu L, Liu T, Zhao Y. Decoy oligodeoxynucleotides, polysaccharides, and targeted peptide-functionalized gold nanorods for the combined treatment of rheumatoid arthritis. *Adv Healthc Mater*. 2019;8(20):e1970074.
91. Zhang L, Yang G, Johnson BN, Jia X. Three-dimensional (3D) printed scaffold and material selection for bone repair. *Acta Biomater*. 2019; 84:16-33.
92. Jang JH, Lee EJ. Influence of MXene particles with a stacked-lamellar structure on osteogenic differentiation of human mesenchymal stem cells. *Materials (Basel)*. 2021;14(16):4453.
93. Ryu NE, Lee SH, Park H. Spheroid culture system methods and applications for mesenchymal stem cells. *Cells*. 2019;8(12):1620.
94. Białkowska K, Komorowski P, Bryszewska M, Miłowska K. Spheroids as a type of three-dimensional cell cultures-examples of methods of preparation and the Most important application. *Int J Mol Sci*. 2020;21(17):6225.
95. Jang J, Lee E-J. Rapid formation of stem cell spheroids using two-dimensional MXene particles. *Processes*. 2021;9(6):957.
96. Zhang J, Fu Y, Mo A. Multilayered titanium carbide MXene film for guided bone regeneration. *Int J Nanomedicine*. 2019;14:10091-10103.
97. Awasthi GP, Maharjan B, Shrestha S, et al. Synthesis, characterizations, and biocompatibility evaluation of polycaprolactone-MXene electrospun fibers. *Colloid Surf Physicochem Eng Aspec*. 2020;586: 124282.
98. Huang R, Chen X, Dong Y, et al. MXene composite nanofibers for cell culture and tissue engineering. *ACS Appl Bio Mater*. 2020;3(4): 2125-2131.
99. Yin J, Han Q, Zhang J, et al. MXene-based hydrogels endow polyetheretherketone with effective osteogenicity and combined treatment of osteosarcoma and bacterial infection. *ACS Appl Mater Interfaces*. 2020;12(41):45891-45903.
100. Costa DO, Prowse PDH, Chrones T, et al. The differential regulation of osteoblast and osteoclast activity by surface topography of hydroxyapatite coatings. *Biomaterials*. 2013;34(30):7215-7226.
101. Li KW, Yan JH, Wang CH, Bi L, Zhang Q, Han YS. Graphene modified titanium alloy promote the adhesion, proliferation and

osteogenic differentiation of bone marrow stromal cells. *Biochem Biophys Res Commun*. 2017;489(2):187-192.
102. Gu M, Lv LW, Du F, et al. Effects of thermal treatment on the adhesion strength and osteoinductive activity of single-layer graphene sheets on titanium substrates. *Sci Rep*. 2018;8:8141.
103. Ren N, Li JH, Qiu JC, et al. Growth and accelerated differentiation of mesenchymal stem cells on graphene-oxide-coated titanate with dexamethasone on surface of titanium implants. *Dent Mater*. 2017; 33(5):525-535.
104. Kumar S, Parekh SH. Linking graphene-based material physicochemical properties with molecular adsorption, structure and cell fate. *Commun Chem*. 2020;3(1):1-11.
105. Wei CB, Liu ZF, Jiang FF, Zeng BH, Huang MD, Yu DS. Cellular behaviours of bone marrow-derived mesenchymal stem cells towards pristine graphene oxide nanosheets. *Cell Prolif*. 2017;50(5): e12367.
106. Cui D, Kong N, Ding L, Guo Y, Yang W, Yan F. Ultrathin 2D titanium carbide MXene (Ti(3) C(2) T(x)) nanoflakes activate WNT/HIF-1α-mediated metabolism reprogramming for periodontal regeneration. *Adv Healthc Mater*. 2021;10(22):e2101215.
107. Zhang WJ, Chang Q, Xu L, et al. Graphene oxide-copper nanocomposite-coated porous CaP scaffold for vascularized bone regeneration via activation of Hif-1α. *Adv Healthc Mater*. 2016;5 (11):1299-1309.
108. Souza JCM, Sordi MB, Kanazawa M, et al. Nano-scale modification of titanium implant surfaces to enhance osseointegration. *Acta Biomater*. 2019;94:112-131.
109. Albrektsson T, Wennerberg A. On osseointegration in relation to implant surfaces. *Clin Implant Dent Relat Res*. 2019;21(1):4-7.
110. Bosshardt DD, Chappuis V, Buser D. Osseointegration of titanium, titanium alloy and zirconia dental implants: current knowledge and open questions. *Periodontol 2000*. 2017;73(1):22-40.
111. Guglielmotti MB, Olmedo DG, Cabrini RL. Research on implants and osseointegration. *Periodontol 2000*. 2019;79(1):178-189.
112. Zuo W, Yu L, Lin J, Yang Y, Fei Q. Properties improvement of titanium alloys scaffolds in bone tissue engineering: a literature review. *Ann Transl Med*. 2021;9(15):1259.
113. Jang J-H, Oh J-S, Lee E-J, Han C-M. Electophoretically deposition of Ti3C2 on titanium surface for hard tissue implant applications. *Coatings*. 2021;11(7):761.
114. Zhang L, Haddouti EM, Welle K, et al. The effects of biomaterial implant wear debris on osteoblasts. *Front Cell Dev Biol*. 2020; 8:352.
115. Pajarinen J, Lin TH, Nabeshima A, et al. Mesenchymal stem cells in the aseptic loosening of total joint replacements. *J Biomed Mater Res A*. 2017;105(4):1195-1207.
116. Sun KY, Wu Y, Xu J, et al. Niobium carbide (MXene) reduces UHMWPE particle-induced osteolysis. *Bioact Mater*. 2022;8: 435-448.
117. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. *J Clin Periodontol*. 2018;45(20):S1-S8.
118. Charalampakis G, Leonhardt Å, Rabe P, Dahlén G. Clinical and microbiological characteristics of peri-implantitis cases: a retrospective multicentre study. *Clin Oral Implants Res*. 2012;23(9):1045-1054.
119. Robitaille N, Reed DN, Walters JD, Kumar PS. Periodontal and peri-implant diseases: identical or fraternal infections? *Mol Oral Microbiol*. 2016;31(4):285-301.
120. Yang C, Luo Y, Lin H, Ge M, Shi J, Zhang X. Niobium carbide MXene augmented medical implant elicits bacterial infection elimination and tissue regeneration. *ACS Nano*. 2021;15(1):1086-1099.
121. Hämmerle CH, Karring T. Guided bone regeneration at oral implant sites. *Periodontol 2000*. 2000;17:151-175.
122. Retzepi M, Donos N. Guided bone regeneration: biological principle and therapeutic applications. *Clin Oral Implants Res*. 2010;21(6): 567-576.
123. Schlegel AK, Mohler H, Busch F, Mehl A. Preclinical and clinical studies of a collagen membrane (bio-Gide[R]). *Biomaterials*. 1997; 18(7):535-538.
124. Chen K, Chen Y, Deng Q, et al. Strong and biocompatible poly(lactic acid) membrane enhanced by Ti3C2Tz (MXene) nanosheets for guided bone regeneration. *Mater Lett*. 2018;229:114-117.
125. Fu Y, Zhang J, Lin H, Mo A. 2D titanium carbide(MXene) nanosheets and 1D hydroxyapatite nanowires into free standing nanocomposite membrane: in vitro and in vivo evaluations for bone regeneration. *Mater Sci Eng C Mater Biol Appl*. 2021;118:111367.
126. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers*. 2017;3:17038.
127. Slots J. Periodontitis: facts, fallacies and the future. *Periodontol 2000*. 2017;75(1):7-23.
128. Han J, Menicanin D, Gronthos S, Bartold PM. Stem cells, tissue engineering and periodontal regeneration. *Aust Dent J*. 2014;59(1): 117-130.
129. Kim BS, Mooney DJ. Development of biocompatible synthetic extracellular matrices for tissue engineering. *Trends Biotechnol*. 1998; 16(5):224-230.
130. Kim HD, Amirthalingam S, Kim SL, Lee SS, Rangasamy J, Hwang NS. Biomimetic materials and fabrication approaches for bone tissue engineering. *Adv Healthc Mater*. 2017;6(23):1700612.
131. Jimenez-Andrade JM, Mantyh WG, Bloom AP, Ferng AS, Geffre CP, Mantyh PW. Bone cancer pain. *Ann N Y Acad Sci*. 2010;1198: 173-181.
132. Papagelopoulos PJ, Mavrogenis AF, Savvidou OD, Benetos IS, Galanis EC, Soucacos PN. Pathological fractures in primary bone sarcomas. *Injury*. 2008;39(4):395-403.
133. Tan B, Tang Q, Zhong Y, et al. Biomaterial-based strategies for maxillofacial tumour therapy and bone defect regeneration. *Int J Oral Sci*. 2021;13(1):9.
134. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: current treatment and a collaborative pathway to success. *J Clin Oncol*. 2015;33(27):3029-3035.
135. Sulman EP, Ismaila N, Armstrong TS, et al. Radiation therapy for glioblastoma: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology guideline. *J Clin Oncol*. 2017;35(3):361-369.
136. Pan S, Yin J, Yu L, et al. 2D MXene-integrated 3D-printing scaffolds for augmented osteosarcoma phototherapy and accelerated tissue reconstruction. *Adv Sci (Weinh)*. 2020;7(2):1901511.
137. Yang Q, Yin H, Xu T, et al. Engineering 2D mesoporous silica@MXene-integrated 3D-printing scaffolds for combinatory osteosarcoma therapy and NO-augmented bone regeneration. *Small*. 2020; 16(14):e1906814.
138. Carano RA, Filvaroff EH. Angiogenesis and bone repair. *Drug Discov Today*. 2003;8(21):980-989.
139. Saran U, Gemini Piperni S, Chatterjee S. Role of angiogenesis in bone repair. *Arch Biochem Biophys*. 2014;561:109-117.
140. Yin J, Pan S, Guo X, et al. Nb(2)C MXene-functionalized scaffolds enables osteosarcoma phototherapy and angiogenesis/osteogenesis of bone defects. *Nano Lett*. 2021;13(1):30.
141. Tahara RK, Brewer TM, Theriault RL, Ueno NT. Bone metastasis of breast cancer. *Adv Exp Med Biol*. 2019;1152:105-129.
142. Yin JJ, Pollock CB, Kelly K. Mechanisms of cancer metastasis to the bone. *Cell Res*. 2005;15(1):57-62.
143. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. *Int J Colorectal Dis*. 2019;34(1):13-25.
144. Sugie T. Immunotherapy for metastatic breast cancer. *Chin Clin Oncol*. 2018;7(3):28.

145. Ralli M, Botticelli A, Visconti IC, et al. Immunotherapy in the treatment of metastatic melanoma: current knowledge and future directions. *J Immunol Res*. 2020;2020:9235638.
146. He C, Yu L, Yao H, Chen Y, Hao Y. Combinatorial photothermal 3D-printing scaffold and checkpoint blockade inhibits growth/metastasis of breast cancer to bone and accelerates osteogenesis. *Adv Funct Mater*. 2021;31(10):2006214.
147. Fraczek-Szczypta A. Carbon nanomaterials for nerve tissue stimulation and regeneration. *Mater Sci Eng C Mater Biol Appl*. 2014;34:35-49.
148. Guo R, Xiao M, Zhao W, et al. 2D Ti(3)C(2)T(x)MXene couples electrical stimulation to promote proliferation and neural differentiation of neural stem cells. *Acta Biomater*. 2020;139:105-117.
149. Wychowaniec JK, Litowczenko J, Tadyszak K, et al. Unique cellular network formation guided by heterostructures based on reduced graphene oxide - Ti(3)C(2)T(x) MXene hydrogels. *Acta Biomater*. 2020;115:104-115.
150. Driscoll N, Richardson AG, Maleski K, et al. Two-dimensional Ti(3)C(2) MXene for high-resolution neural interfaces. *ACS Nano*. 2018;12(10):10419-10429.
151. Fu X, Yang H, Li Z, et al. Cation-induced assembly of conductive MXene fibers for wearable heater, wireless communication, and stem cell differentiation. *ACS Biomater Sci Eng*. 2021.
152. Driscoll N, Maleski K, Richardson AG, et al. Fabrication of Ti3C2 MXene microelectrode arrays for in vivo neural recording. *J Vis Exp*. 2020;156:e60741.
153. Xu B, Zhu M, Zhang W, et al. Ultrathin MXene-micropattern-based field-effect transistor for probing neural activity. *Adv Mater*. 2016;28(17):3333-3339.
154. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol*. 2018;15(4):230-240.
155. Thomas H, Diamond J, Vieco A, et al. Global atlas of cardiovascular disease 2000-2016: the path to prevention and control. *Glob Heart*. 2018;13(3):143-163.
156. Rowe WJ. Extraordinary unremitting endurance exercise and permanent injury to normal heart. *Lancet*. 1992;340(8821):712-714.
157. Cowger JA. Addressing the growing U.S. donor heart shortage: waiting for Godot or a transplant? *J Am Coll Cardiol*. 2017;69(13):1715-1717.
158. Wilhelm MJ. Long-term outcome following heart transplantation: current perspective. *J Thorac Dis*. 2015;7(3):549-551.
159. Marion MH, Bax NA, Spreeuwel AC, van der Schaft DW, Bouten CV. Material-based engineering strategies for cardiac regeneration. *Curr Pharm Des*. 2014;20(12):2057-2068.
160. D RA, Sink E, Narayan SP, Abdel-Hafiz M, Mestroni L, Peña B. Nanomaterials for cardiac tissue engineering. *Molecules* 2020;25(21):5189.
161. Basara G, Saeidi-Javash M, Ren X, et al. Electrically conductive 3D printed Ti(3)C(2)T(x) MXene-PEG composite constructs for cardiac tissue engineering. *Acta Biomater*. 2020;139:179-189.
162. Ye G, Wen Z, Wen F, et al. Mussel-inspired conductive Ti(2)C-cryogel promotes functional maturation of cardiomyocytes and enhances repair of myocardial infarction. *Theranostics*. 2020;10(5):2047-2066.
163. Xu Q, Ding L, Wen Y, et al. High photoluminescence quantum yield of 18.7% by using nitrogen- doped Ti3C2 MXene quantum dots. *J Mater Chem C*. 2018;6(24):6360-6369.
164. Xue Q, Zhang H, Zhu M, et al. Photoluminescent Ti3C2 MXene quantum dots for multicolor cellular imaging. *Adv Mater*. 2017;29(15):1604847.
165. Liu MW, He Y, Zhou J, Ge YL, Zhou JG, Song GW. A "naked-eye" colorimetric and ratiometric fluorescence probe for uric acid based on Ti3C2 MXene quantum dots. *Anal Chim Acta*. 2020;1103:134-142.
166. Shao J, Zhang J, Jiang C, Lin J, Huang P. Biodegradable titanium nitride MXene quantum dots for cancer phototheranostics in NIR-I/II biowindows. *Chem Eng J*. 2020;400:126009.
167. Rafieerad A, Yan WA, Alagarsamy KN, et al. Fabrication of smart tantalum carbide MXene quantum dots with intrinsic immunomodulatory properties for treatment of allograft vasculopathy. *Adv Funct Mater*. 2021;31(46):2106786.
168. Rafieerad A, Yan W, Sequiera GL, et al. Application of Ti3C2 MXene quantum dots for immunomodulation and regenerative medicine. *Adv Healthc Mater*. 2019;8(16):1900569.
169. Mandrycky C, Wang Z, Kim K, Kim DH. 3D bioprinting for engineering complex tissues. *Biotechnol Adv*. 2016;34(4):422-434.
170. Rastin H, Zhang B, Mazinani A, et al. 3D bioprinting of cell-laden electroconductive MXene nanocomposite bioinks. *Nanoscale*. 2020;12(30):16069-16080.
171. Ciou JH, Li S, Lee PS. Ti(3) C(2) MXene paper for the effective adsorption and controllable release of aroma molecules. *Small*. 2019;15(38):e1903281.
172. Lukatskaya MR, Mashtalir O, Ren CE, et al. Cation intercalation and high volumetric capacitance of two-dimensional titanium carbide. *Science*. 2013;341(6153):1502-1505.
173. Mashtalir O, Naguib M, Mochalin VN, et al. Intercalation and delamination of layered carbides and carbonitrides. *Nat Commun*. 2013;4:1716.
174. Ren CE, Hatzell KB, Alhabeb M, Ling Z, Mahmoud KA, Gogotsi Y. Charge- and size-selective ion sieving through Ti3C2Tx MXene membranes. *J Phys Chem Lett*. 2015;6(20):4026-4031.
175. Meng F, Seredych M, Chen C, et al. MXene sorbents for removal of urea from dialysate: a step toward the wearable artificial kidney. *ACS Nano*. 2018;12(10):10518-10528.
176. Zhao Q, Seredych M, Precetti E, et al. Adsorption of uremic toxins using Ti(3)C(2)T(x) MXene for dialysate regeneration. *ACS Nano*. 2020;14(9):11787-11798.

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