Biomedical Applications of MXene-Integrated Composites: Regenerative Medicine, Infection Therapy, Cancer Treatment, and Biosensing

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MXenes (viz., transition metal carbides, carbonitrides, and nitrides) have emerged as a new subclass of 2D materials. Due to their outstanding physicochemical and biological properties, MXenes have gained much attention in the biomedical field in recent years, including drug delivery systems, regenerative medicine, and biosensing. Additionally, the incorporation of MXenes into hydrogels has garnered significant interest in biomedical engineering as an electroactive and mechanical nanoreinforcer capable of converting nonconductive scaffolds into excellent conductors of electricity with an impressive effect on mechanical properties for the engineering of electroactive organs and tissues such as cardiac, skeletal muscle, and nerve. However, many questions and problems remain unresolved that need to be answered to usher these 2D materials toward their true destiny. Thus, this review paper aims to provide an overview of the design and applications of MXene-integrated composites for biomedical applications, including cardiac tissue engineering, wound healing, infection therapy, cancer therapy, and biosensors. Moreover, the current challenges and limitations of utilizing MXenes in vivo are highlighted and discussed, followed by its prospects as a guideline toward possible various futuristic biomedical applications. This review article will inspire researchers, who search for properties, opportunities, and challenges of using this 2D nanomaterial in biomedical applications.

1. Introduction

Advances in disease therapy and biomedicine flourished again with the introduction of 2D materials.[1,2] The unconventional properties of 2D nanomaterials were considered after receiving the 2010 Nobel Prize.[3,4] These nanomaterials offered better properties, such as more remarkable performance, flexibility, and higher compatibility than a single element of graphene.[5] Second, their ultrathin thickness and 2D morphological structure have unique physical, chemical, and electronic properties compared to their congeries types.[5–7]

MXenes (viz., transition metal carbides, carbonitrides, and nitrides) have emerged as a new subclass of 2D materials. They are generated via MAX phases (viz., selective elements etching from their 3D layered ternary carbides/nitrides analogs). Their structures can be formulated as $M_{n+1}AX_n^T_x$ ($n = 1–3$), where $M$ denotes transition metals, $A$ (main-group elements, predominantly, 13 and 14 groups), $X$ (carbon and/or nitrogen), and $T$ (the surface termination groups such as ...
fluorine, oxygen, chlorine, and hydroxyl), and $x$ (the number of surface functionalities). [9]

MXenes’s precursor type (viz., MAX) affects the product’s ability and the synthesis routes. MXenes can be fabricated from their MAX phase so that the M-A (metal type) connection can be broken by the etching process and causing A removal. Various factors, such as the type/concentration of etching, temperature/duration of the etching process, and environmental conditions, affect the selective etching process. The required conditions for the etching process depend on the type of MAX precursor. The type of the selected element and the amount of energy required to break the M-A bond (viz., exfoliation) determine the chemical etchant for exfoliation. [10–12]

Here, we discuss the unexplored and enormous possibilities of MXene-integrated composite biomaterials for biomedical applications. In fact, the innovation of this review article over the existing reviews is that the previous ones only focused on the Mxene nanosheet alone. Herein, we will discuss how integrating the MXenes with other components, including nanoparticles (NPs), nanosheets, and polymers can affect the physicochemical properties of the MXenes alone compounds, such as dispersion and photothermal activities. Furthermore, we will discuss how such composites might alter the biobehavior of MXene nanosheets, such as biocompatibility, biodegradability, and efficiency in biomedical applications. To this end, we will mainly focus on regenerative medicine (cardiac, bone, and skin regeneration), infection therapy, and cancer treatments, as we believe these areas present the most promising applications of MXenes. In addition, a special section of the current review is the design and fabrication of MXene-based sensors and wearable devices for biosensing applications. Finally, the research community’s future directions and challenges that need to be pursued are discussed. We believe that such an assembly of immense review articles, including topics related to MXene-based materials, will be a noteworthy guide for future development in biomedicine.

2. MXene-Integrated Nanocomposites

MXenes are superb pretenders for a wide domain of biomedical applications. The functions and unique features of MXenes (e.g., conductivity, large surface area, hydrophilicity, 2D geometry, and particle size regulation) have also been able to gait into the world of nanohybride and nanocomposite. Such capabilities can improve their poor oxidative stability, low target specificity, biodegradability, and biocompatibility in physiological environments. [13,14] The surface of MXene nanosheets provides a substrate for the growth of/and deposition of various types of organic and inorganic compounds in the forms of molecule, chain, and nanoparticles (Figure 1). The surface-functionalization and hybridization can be conducted in situ and ex situ methods. In addition to their enhanced physiological features, the surface manipulation strategies can boost other properties of the 2D-nanosheets such as conductivity, photosensitivity, and photothermal ability. To achieve these aims, the surface of MXene nanosheets has been functionalized by soybean phospholipid, [15] poly (vinyl alcohol), [16] poly(ethylene glycol), [17,18] bovine serum albumin, [19] and inorganic nanoparticles (such as gold, [20,21] iron oxide, [15] manganese oxide). [22,23] Moreover, other 2D nanostructures such as reduced graphene oxide nanosheets can be hybridized with the MXene nanosheets to induce synergistic conductivity and thermal behavior. [24] Besides, the MXenes can be employed in the bioglass structures to induce photosensitivity properties to the final scaffold. [25] Different techniques have also been employed to process the MXene-based nanocomposites into various shapes and architectures, such as membrane, nanofiber, porous material, polymeric microparticles, and 3D-printed products (Figure 1). [26–28]

3. Regenerative Medicine

Organ failure and tissue damage can occur due to diseases or traumas, resulting in millions of deaths each year around the world. Tissue engineering employs scaffold/biomaterials, cells, and biological molecules to restore or improve tissue and organ function. [29] Among the several scaffold biomaterials that have been used in tissue engineering, hydrogels have garnered the most interest due to their adaptability, biocompatibility, and biodegradability, as well as their ability to generate a biomimetic 3D microenvironment to support cell activity. [30] To promote electrophysiological properties of wound dressing materials (e.g., hydrogels), they can be integrated with conductive particles like MXenes. [31–33] Studies have shown that MXene-based biomaterials possess anti-inflammatory and immunomodulatory properties, making them excellent for tissue engineering applications. [34,35] In this section, various applications of MXenes-based nanocomposites in tissue engineering and regenerative medicine are discussed in detail (Table 1).
### 3.1. Wound Healing

The skin has the largest surface area on the outside of our bodies to protect internal organs from damage, infection, ultraviolet radiation, and high temperature. Therefore, any defects in the skin can initiate various ailments such as wound infection, which can affect human health.[44,45] Multiple cell types within the epidermis, dermis, and hypodermis layers must be coordinated in multistep processes to repair skin wounds. Skin wound healing is a typical process in the body in response to an injury, consisting of four highly integrated and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling. All these steps must occur precisely for successful wound healing.[46] A good dressing for wound healing should provide constant temperature, protect cell proliferation and migration, and possess antimicrobial properties.[47–49] Hydrogel-based dressings have attracted significant attention for wound healing when subjected to external electrical stimulation.[50] Based on such grounds, Yang and colleagues fabricated a hydrogel dressing made of regenerated bacterial cellulose and MXene that could accelerate wound healing when subjected to external electrical stimulation.[51] As shown in Figure 2A, the cellulose/MXene composite hydrogels were produced through chemical (covalent cross-linking) and physical (hydrogen bonding) reactions. The results revealed that combining cellulose/MXene hydrogels with external electrical stimulation significantly influenced cell activity. Furthermore, results from in vivo rat experiment showed that this system could promote tissue regeneration and accelerate the process of wound healing in this in vivo experiment, an external electric field from 0 to 400 mV was applied using...
copper electrodes on the hydrogel dressing. The macroscopic images exhibited the wounds treated by cellulose/MXene + electric field (100 mV mm\(^{-1}\)) had smaller surfaces than the other groups during the period of treatment (Figure 2C). Histological analysis of healed tissues by H&E and Masson trichrome staining as well as the immunofluorescent staining for CD31 revealed that the MXene-integrated hydrogels with or without electric field caused the formation of new blood vessels, normal epithelium, less inflammation, higher density of fibroblasts, and better wound healing effect than a commercial dressings and antibacterial strategies.

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<th>Table 1. MXene-integrated nanocomposites for regenerative medicine.</th>
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<td>Formulation</td>
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<td>Bioglass@NbSiR</td>
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<td>MXene–amoxicillin–PVA nanofibrous membrane</td>
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<td>Muscle-inspired MXene/PVA hydrogel</td>
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<td>Chitosan–hyaluronate hydrogel@Ti3C2T, MXene nanocomposites</td>
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<td>Nb2C MXene-integrated 3D-printed bone-mimetic scaffold</td>
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3.2. Cardiac Tissue Engineering

Cardiac failure can occur under different conditions and affects nearly 64 million people worldwide.\(^{[52]}\) One of the promising strategies for improving heart tissue regeneration is the design and fabrication of conductive cardiac patches to promote the cardiac patch’s electrophysiological coupling with the host tissue. Many conductive polymers\(^{[31]}\) and particles such as carbon nanotubes,\(^{[53]}\) graphene,\(^{[54]}\) gold nanorods,\(^{[55]}\) and MXenes\(^{[56]}\) have been integrated into a hydrogel or cryogel to enhance electrophysiological properties for cardiac tissue engineering applications. To this end, appropriate alignment of the cardiomyocytes (CMs) is a key factor. This is due to the cardiac tissue’s functionality is highly affected by the myofibrils’ alignment and
their assembly into bundles, as well as the longitudinal shape of the ventricular myocytes and their interconnections. Aerosol jet printing (AJP) is an excellent strategy to achieve cell-scaled printed patterns due to its high resolution as well as its ability to print on both hard and soft tissues. It is well-suited for printing on hydrogels in any shape and generating hybrid tissue structures. In a study the use of the AJP method was reported for preparing MXene-integrated composites as a human cardiac patch. The conductive Ti3C2Tx MXene was printed on polyethylene glycol (PEG) hydrogel in predesigned patterns, and alignment of the human-induced pluripotent stem-cell-derived cardiomyocyte (iCMs) on the engineered electroconductive cardiac patches was studied. To investigate the cell attachment and alignment, Ti3C2Tx was printed on different substrate: glass, GelMA and PEG hydrogels, and among the fabricated scaffolds, Ti3C2Tx MXene-PEG hydrogels displayed excellent alignment of the iCMs with great viability (Figure A). Moreover, it was shown that Ti3C2Tx MXene could be printed on PEG hydrogel in different patterns which enabled cells to be patterned in various shapes. The impact of MXene and patterning on iCM phenotype and maturity, was followed by immunostaining, qRT-PCR, and western blotting techniques after seeding iCM cells on straight line-patterned Ti3C2Tx MXene printed on glass samples adhered to the glass rather than align along the lines. The qRT-PCR analysis results indicated a significant increase in relative mRNA expression of cardiac markers in Hilbert’s curve-patterned samples compared with straight line-patterned glass samples and confirmed improved iCMs maturity (Figure 3C). To assess the contraction kinetics of the cardiac patches, the Ca2+ handling and conduction velocity were examined (Figure 3D,E). The results revealed the synchronous beating rate of the iCMs was improved by integrating Ti3C2Tx MXene into the nonconductive hydrogels. As another instance, injectable shape-memory composite tissue scaffolds were obtained by incorporating Ti3C2 MXene quantum dots into chitosan-based hydrogels for in vitro applications. These scaffolds could support cell survival and proliferation and transfer electrical signals among cells. Therefore, the chitosan–MXene quantum dots composites can be candidates for tissue engineering demands. In a similar work, chitosan based-hydrogels containing Ti3C2 MXene, honey, and 0D fluorescent carbon dots were prepared and used for tissue engineering application. These hydrogels revealed good compatibility with several types of stem cells and anti-inflammatory and antibacterial properties. In another study, Ti3C2Tx nanosheets were added to the reduced graphene oxide hydrogel and explored for different applications, particularly tissue engineering applications.

Figure 2. A) Synthesis scheme of cellulose (rBC)-based hydrogels. B) Confocal microscopy of Live/Dead staining. Scale bar: 100 µm. C) The wound healing process on days 0, 3, 7, and 14 in the different treated groups. Scale bar: 500 µm. D) Histological analysis of healed tissues by H&E, Masson’s trichrome staining, and immunohistochemical staining of CD31+ microvessels at day 14. Blood vessel (blue arrow), fibroblast (yellow arrow), neutrophil (purple arrow), the hair follicle (red arrow), collagen deposition (green arrow), and CD31+ structures (brown). Reproduced with permission. Copyright 2020, Wiley-VCH.
Figure 3. A) Viability percentage of iCMs on patterned Ti$_3$C$_2$T$_x$ MXene on PEG hydrogel. B) Immunostaining characterization of the straight-line patterned MXene printed on glass (On glass), unpatterned Ti$_3$C$_2$T$_x$ MXene (On MXene), and Hilbert’s curve-patterned Ti$_3$C$_2$T$_x$ MXene printed on PEG (Hilbert’s curve); 1) Connexin-43 staining, 2) the sarcomeric alpha-actinin staining, 3) combined Connexin-43 and sarcomeric alpha-actinin staining. C) Relative mRNA expression of cardiac markers MYH7, SERCA2, GJA1, and TNNT2 by qRT-PCR analysis (**: p < 0.01 and n.s. represents nonsignificant). D) A single snapshot from the calcium flux timelapse recording of on-glass sample (left) and the intensity of calcium flux timelapse image (right). E) A single snapshot from calcium flux timelapse recording of Ti$_3$C$_2$T$_x$ MXene-PEG hydrogel (the pattern was divided into 16 groups and each group
3.3. Bone Regeneration

Bone matrix combines organic materials, inorganic minerals, cells, and bioactive factors.\textsuperscript{[60]} Due to poor self-healing capability, bone defect repairing is still one of the most challenging issues in clinical communities.\textsuperscript{[61]} Most of the current bone transplants have drawbacks, such as the difficulty in acquiring adequate connective tissue and the possibility of immunological responses.\textsuperscript{[62,63]} As an alternative, many scaffolds or bone-substitute biomaterials have been developed to reconstruct the defects and regenerate bone tissues.\textsuperscript{[65,66,64]} One of the key requirements of bone tissue engineering is the design and development of tissue engineering scaffolds that recapitulate important characteristics of bone to mimic native bone tissue function and therefore regenerate the damaged tissues.\textsuperscript{[65-67]} In addition to the antibacterial and biocompatibility of Ti\textsubscript{3}C\textsubscript{2} MXene, they have Ca\textsuperscript{2+} binding sites which promote osteogenesis.\textsuperscript{[68,69]} The integrated Ti\textsubscript{3}C\textsubscript{2} MXenes with 3D-printed bioactive glass scaffolds have been utilized for bone tissue regeneration and cancer treatment.\textsuperscript{[70]} In another study, the Ti\textsubscript{3}C\textsubscript{2} MXene film with the capability of in vitro osteogenic differentiation was developed to guide bone tissue regeneration. In vivo studies showed adequate biocompatibility and bone regeneration activity in a rat calvarial bone defect.\textsuperscript{[73]} In another study, incorporating ultralong hydroxyapatite nanowires into the MXene film boosted osteogenic activity (Figure 3F).\textsuperscript{[40]} The in vitro and in vivo studies have demonstrated that the nanocomposite membranes have good biocompatibility and outstanding osteoinductivity. The results also confirmed that the hydroxyapatite nanowire content significantly impacted the physical and mechanical properties of the designed nanocomposite membrane. Moreover, surprising flexibility was found for the nanocomposite containing 10 wt% of hydroxyapatite after multiple folding and wrapping around a plastic rod without any damage (Figure 3G, H).\textsuperscript{[40]} In a recent study, the extrusion-based 3D printing technique was used to fabricate nanocomposite scaffolds based on the Ti\textsubscript{3}C\textsubscript{2}–MXene modified with hydroxyapatite and sodium alginate (Figure 3I). The in vitro biocompatibility and osteogenic activity of these nanocomposite scaffolds (Ti\textsubscript{3}C\textsubscript{2}–MXene modified HA/SA) were studied with the rat bone mesenchymal stem cells (BMSCs). The scaffolds had a relatively rough surface that could improve cell adhesion and migration and proliferation, differentiation, and formation of new bone tissue (Figure 3J). Moreover, the porosity of the designed scaffolds favored the migration of mesenchymal cells, nutrient transport, and vessel ingrowth, providing a favorable osteogenic microenvironment. The SEM images displayed a large number of BMSCs homogeneously adhered to the surface of Ti\textsubscript{3}C\textsubscript{2}–MXene composite scaffolds without an observable change in morphology of BMSCs, confirming the excellent cell adhesion and viability of BMSCs (Figure 3K).\textsuperscript{[27]} Consequently, it was found that the Ti\textsubscript{3}C\textsubscript{2}–MXene modified HA/SA scaffolds could effectively enhance the regeneration of calvarial bone defects, and the bone healing was specifically higher than those without Ti\textsubscript{3}C\textsubscript{2}–MXene incorporation.

4. Infection Therapy

Extensive use of antibiotics has emerged drug-resistant bacteria along with their overuse or misuse.\textsuperscript{[72,73]} In recent years, substantial efforts have been devoted to developing alternative antibacterial materials, such as metal nanoparticles,\textsuperscript{[74,75]} nanoyzemes,\textsuperscript{[76,77]} mesoporous silicas,\textsuperscript{[78]} cationic polymers,\textsuperscript{[79,80]} and many more. MXene nanosheets have shown bactericidal properties that can disrupt the bacterial membrane and induce oxidative stress to kill bacteria.\textsuperscript{[38,81-85]} In 2020, a synergistic antimicrobial agent was launched by conjugating AuNCs to the Ti\textsubscript{3}C\textsubscript{2}T\textsubscript{x} MXene nanosheets (Figure 4).\textsuperscript{[86]} To this end, amine-modified Ti\textsubscript{3}C\textsubscript{2}T\textsubscript{x} (MXene-NH\textsubscript{2}) was synthesized via (3-aminopropyl) triethoxysilane and Ti\textsubscript{3}C\textsubscript{2}T\textsubscript{x}. Then, using carbodiimide crosslinker chemistry, Au-functionalized MXene nanocomposites were prepared by chemically bonding MXene-NH\textsubscript{2} to COOH-functionalized AuNCs. The mechanistic investigation demonstrated that the antibacterial efficacy of the 2D MXenes noticeably was improved after the Au conjugation.\textsuperscript{[86]} The sharp MXene nanosheets physically damage the bacterial membrane, thus allowing the nanocomposites to internalize inside bacteria. Not only MXene but also Au nanostructures caused oxidative stress in bacteria by generating reactive oxygen species (ROS) (Figure 4A). On the other hand, such ROS reservoirs resulted in effective lipid peroxidation (Figure 4B), which significantly contributed to increased bacterial membrane damage for increased membrane breakdown. Moreover, the localized ROS at high concentrations could oxidize and destroy bacterial DNA, thus ultimately leading to the killing of bacteria (Figure 4C).\textsuperscript{[86]} Interestingly, after the construction of two types of planar and crumpled MXene–Au nanocomposite structures (designated as p-MXene and c-MXene), it was found that the crumpled structures effectively inhibited biofilm formation in comparison with the planar ones(Figure 4D–G). This phenomenon was attributed to the hydrophobic surface of the c-MXene to prevent bacterial attachment as well as their high surface area, endowing them with a higher density of bactericides. Although in vivo study was not conducted, this synergistic effect stemming from the Au-conjugated MXenes holds great promise to design and fabricate novel but effective MXene-based nanocomposites against bacterial infections.

MXene exhibits antibacterial properties through chemical and physical mechanisms. Among them, induction of oxidative stress is widespread. However, some studies have indicated it is ineffective for many bacteria. On the other hand, the poor...
quality of wound healing and skin regeneration has been a challenge for those wounds infected with bacteria, particularly drug-resistance bacteria. Therefore, combating bacterial infection while facilitating wound healing is rational and ideal. However, achieving these two goals together is not very likely without utilizing bioactive agents or antibiotics. To this end, polydopamine-coated 2D Ti$_3$C$_2$T$_x$ MXenes nanosheets (MXene@PDA) were integrated into a polymeric matrix composed of branched polyglycerol-ethyleneimine) (PGE)/oxidized hyaluronic acid (HCHO) to create multifunctional scaffolds (HPEM) for the treatment of wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) (Figure 5A–C).[38] The HCHO supplies the main matrix of the scaffold, MXene@PDA and PGE can serve as an excellent conductivity, antibacterial activity, and tissue adhesive ability to stimulate the infected wound healing and skin regeneration. The authors speculated that the dynamic Schiff-base bonds between PGE and HCHO conferred self-healing capability to the HPEM scaffolds (Figure 5D,E). Moreover, the HPEM scaffolds showed an antibacterial efficiency of around 99.03% against *Escherichia coli*, *S. aureus*, and MRSA (Figure 5F), rapid hemostatic capability (Figure 5G), and accelerated healing of the infected wound.
These enhancements were due to HPEM’s anti-infection effect and ability to promote cell proliferation and angiogenesis. This resulted in the formation of granulation tissue and vascular endothelial differentiation, upregulation of alpha-smooth muscle actin (α-SMA) and platelet endothelial cell adhesion molecules (also known as CD31), and collagen deposition. \(^{[38]}\)

MXenes have shown great potential in photothermal therapy (PTT). Therefore, they can eradicate bacteria physically without concern for drug-resistance development. \(^{[81]}\) In a recent example, Fan and co-workers expressed that the photothermal properties of MXenes could damage surrounding tissues, and the residual survived bacterial will reproliferate after the near-infrared (NIR) region irradiation. \(^{[87]}\) Therefore, they proposed the combination of photothermal and antibacterial agents to deal more effectively against bacterial infection. In this regard, Ti\(_3\)C\(_2\)T\(_x\) MXene was employed as a substrate and PTT agent. Additionally, it was used to mitigate the cytotoxicity...
of silver nanoparticles (Ag NPs) and obtain high potency and long-term antibacterial activity. The Ag/Ti3C2Tx composite was synthesized through HF etching and tetramethylammonium hydroxide (TMAOH) delamination of Ti3AlC2 MAX. It is noteworthy that the Ag ions, as antibacterial agents, interacted electrostatically with the negatively charged Ti3C2Tx MXene (Figure 6). To confirm photothermal conversion efficiency of the composite, it was exposed to 808 nm irradiation for 300 s and on-off time was recorded (Figure 6A). Compared to the Ti3C2Tx MXene, the composite increased the temperature less with the same concentration (200 µg mL−1). This hyperthermia of the pure MXene is not suitable for in vivo application and may cause side effects on the surrounding tissues. Therefore, they expressed that Ag/Ti3C2Tx composite had sufficient photothermal conversion efficiency for the study. It was exhibited that the composite had antibacterial activity against both Gram-positive S. aureus and Gram-negative E. coli bacteria. As shown in Figure 6B, the composite exhibited a synergistic impact on E. coli growth suppression, with improved antibacterial activities under NIR irradiation at a concentration of 100–200 µg mL−1 compared to the other groups. In order to perform in vivo analysis and appropriate administration of Ag, Ag/Ti3C2Tx, and Ti3C2Tx MXene on the S. aureus infected mice skin model, the samples were embedded in poly(carboxybetaine acrylamide) (PCB). The hydrogel was constructed by dissolving the carboxybetaine (CB) monomer and N,N-methylenebisacrylamide as the crosslinker in NaCl (1 M). The samples were added to the solution, and after sonication and vortexing with ammonium persulfate, the Ag, Ag/Ti3C2Tx, and Ti3C2Tx MXene-embedded PCB hydrogel were obtained and finally hydrated in phosphate buffer saline (PBS) buffer. Figure 6C displays the photographs of the wounds on the dorsum of Balb/c mice. Due to synergistic antimicrobial action, the Ag/Ti3C2Tx hydrogels + NIR induced complete wound healing within 15 days. In the initial days from 0 to 10, the control group and Ag hydrogels did not show effective infection inhibition and wound healing but showed a rapid reduction in wound size from day 3 to 15. The reduction of wound area in all groups was measured on the 7th and 15th days and confirmed the anti-infection strength of Ag/Ti3C2Tx hydrogels compared to other groups (Figure 6D). In the wound healing process, cell proliferation and tissue regeneration also occur. To monitor epidermis regeneration and epithelial migration, the granulation tissue was observed on day 15 (Figure 6E). The authors reported that the granulation layer in Ag/Ti3C2Tx and Ti3C2Tx hydrogel groups was complete and thicker, and the treatment effect of Ag/Ti3C2Tx hydrogels was three times greater than that of the control or Ag groups. Several recent studies have also indicated that changing the amount of MXene in the nanocomposite structure could adjust the biocidal properties of the formed hydrogel. In another study, 2D Ti3C2Tx MXene flakes were prepared and incorporated into a chitosan-hyalurionate (CH/SHA/Ti3C2Tx) matrix (31). The impact of a composite containing varying concentrations of MXene was investigated using three bacterial strains, i.e., gram-negative E. coli, gram-positive S. aureus, and Bacillus sp. The results showed that the biocidal property of the nanocomposites with varying amounts of MXene depended on the type of bacteria. Up to 90% growth

![Figure 6. A) Photothermal conversion efficiency of the Ti3C2Tx and Ag/Ti3C2Tx composite upon 808 nm irradiation for 300 s. B) Antibacterial activity of Ag, Ti3C2Tx, and Ag/Ti3C2Tx. Photographs of bacterial growth with or without NIR irradiation for 15 min (808 nm, 1.5 W cm−2). C) Photographs showing wound infection and healing process with the treatment of Ag/Ti3C2Tx hydrogels. D) The reduction of wound area of different groups on day 7 and day 15. E) The effect of the different treatments on the granulation tissue thickness at day 15. Reproduced with permission. (87) Copyright 2020, The Royal Society of Chemistry.](image-url)
inhibition was observed for all the strains in the presence of a small amount of the Ti$_3$C$_2$T$_x$ MXene nanosheet. Another area of interest for MXenes is their utilization in medical implants. The surface of medical implants and indwelling devices are tremendous substrates for invading bacteria to adhere and form a biofilm. This type of infection is another global public health concern due to the massive utilization of these medical implants. Therefore, coating implantable devices with multiple antimicrobial modalities is an alternative way to inhibit or disrupt biofilm formation and face a low risk of bacterial resistance.[88,89] MXene nanosheets are promising safe candidates for surface modification of implants to bring anti-biofilm performance to the implantable devices. The antimicrobial feature of MXene nanosheets is driven by their atomic structure, ultrathin thickness, and photothermal properties.[90] For instance, it was shown that Nb$_2$C MXene 2D nanosheets exhibited high photothermal-conversion performance. They could gradually degrade in the hydrogen peroxide-rich infectious microenvironment, thus causing a bacteria-killing effect.[91,92] Moreover, the Nb$_2$C MXenes, as a free-radical scavenger, could recover hematopoietic cells after ionizing radiation. Altogether, the Nb$_2$C MXenes could represent simultaneous antimicrobial activity and wound healing promotion. As a result, a therapeutic composite made of surface-modified titanium plates by Nb$_2$C nanosheets (Nb$_2$C@TP, also called NTP) (Figure 7A) was fabricated.[93] The engineered NTP showed a multimodal antimicrobial activity. It could activate the accessory gene regulator to prevent adherence of bacteria and, therefore, attenuate biofilm attachment. It was demagnetized that bacteria death by downregulation of metabolism pathways such as the phosphotransferase system and the tricarboxylic acid cycle was conducted by the Ti-modified Nb$_2$C nanosheets. Through photothermal treatment in the second near-infrared regime (NIR-II, 1000–1700 nm), it could even kill planktonic bacteria (hyperthermia sensitive microorganisms) (Figure 7B–E).[94] Infections caused by bare implantable devices often activate proinflammatory reactions, leading to excessive ROS production.[95] Consequently, this causes normal tissue-damaging and delayed tissue repairing. Interestingly, the Ti-modified Nb$_2$C nanosheets reduced proinflammatory responses and protected tissues from excess ROS produced in the infectious milieu by the ROS scavenging property of the nanosheets. Moreover, in vivo investigations revealed that when Ti-modified Nb$_2$C nanosheets were used as an antibacterial agent, a fast wound temperature recovery and a minor infection area were observed in the mice-bearing infected wounds under NIR irradiation (Figure 7F, G).[96]

5. Cancer Diagnosis and Therapy

Nanocomposites, constructed from two or more constituent materials, have attracted ever-increasing attention.[97] Given the unique structural, metallic conductivity, rich surface chemistry, wide surface area, biocompatibility, hydrophilicity, and particle size tunability, 2D MXenes nanomaterials have found importance for fabricating multifunctional nanocomposites.[88,94,95] Despite their widespread use, MXenes are subject to significant oxidative deterioration, limiting their utility, particularly in biological applications. For example, in the case of Ti-based MXenes, rapid degradation into titanium dioxide can disrupt the biobehavior of the nanosheets. Defective sites of the 2D sheets are mainly responsible for their oxidative degradation reactions in aqueous environments.[96] Thus, it is critical to improving the oxidation stability of MXenes nanosheets to extend their shelf life in practical applications. Although many efforts have been made to enhance the dispersity of MXenes, including freezing aqueous MXene dispersions at a lower temperature (~20 °C),[97] their storage in organic solvents,[98] eliminating the step of ultrasonication to decrease density of defective sites,[94,99] controlling synthesis parameters (e.g., chemical etching conditions, temperature, and pH),[96,99] however, the design and fabrication of MXene-based nanocomposites is an appropriate method to overcome the poor stability in physiological environments.[14,100–102] For example, W$_{1.13}$C-BSA nanocomposite was prepared through surface modification of the nanosheets by BSA to improve their stability in the physiological environment.[19] Through van der Waals attractive interactions and/or hydrogen bonding, BSA, a bioactive macromolecule, functionalized the surface of W1.33C nanosheets. It was shown that the produced nanosheets displayed high dispersity in various physiological solvents such as PBS, cell culture medium, and whole blood diluent. The work significantly expanded the biomedical applications and offered the method as a new paradigm to achieve applicable MXenes through surface engineering. Moreover, rich functional groups at the surface of MXenes allow them to readily be hybridized with other materials, such as surface-superparamagnetic iron oxide,[15,17] g-C$_3$N$_4$,[100,104] MnO$_x$,[22,23] zinc oxide,[105] mesoporous silica nanoparticles,[106] Au nanoclusters[21,86] or polymers,[107–110] to construct advanced functional nanocomposites with advanced therapeutic functionality to realize more functionalities, including a combination of photo and chemodynamic therapy and multimodal imaging performances, which is not attainable by single MXene nanosheets.[111,112] Table 2 represents some examples of MXene-integrated nanocomposites for cancer therapy.

In a study, manganese oxide/tantalum carbide (MnO$_x$/Ta$_2$C$_3$) nanocomposites were constructed by a surface engineering strategy for multiple imaging-guided PTT of cancer. The nanocomposites acted as desirable contrast agents for photothermal imaging and T1-weighted MRI imaging.[22] As shown in Figure 8A, a two-step exfoliation process was carried out to construct nanosized 2D Ta$_2$C$_3$ MXenes. First, the bulk MAX-phase of Ta$_2$C$_3$ (i.e., Ta$_2$AlC$_3$) was sintered at high temperature, and then the middle Al layer was removed by 40% HF solution as an etchant. In order to harvest nanosized 2D Ta$_2$C$_3$ ultrathin nanosheets, sonication was utilized. The surface-exposed hydroxyl groups of Ta$_2$C$_3$ MXenes served as reducing sites for in situ growing of MnO$_x$ nanoparticles on their surfaces by KMnO$_4$ as substrate. Compared to graphene oxide (GO) commonly employed in PTT, the extinction coefficient of MnO$_x$/Ta$_2$C$_3$ nanosheet was much higher than GO (=2.5-fold) at 808 nm.[24] In vitro, photothermal studies on a solution of MnO$_x$/Ta$_2$C$_3$ nanosheets showed that the maximum temperature of the aqueous elevated up to 49 and 65 °C at the power density of 1.5 and 2.0 W cm$^{-2}$, respectively, providing a guarantee for further in vivo tumor ablation.
Figure 7. A) Illustrative scheme of the Ti-modified Nb₂C nanosheets (Nb₂C@TP (NTP)) synthesis. B-C) TEM images of planktonic bacteria in different groups, including *E. coli* and *S. aureus*. NIR irradiation for 5, 10, and 20 min was denoted as NIR5, NIR10, and NIR20. D) Bacterial lactate dehydrogenase (LDH) release rate after different treatments. E) Ortho-nitrophenyl-β-D-galactoside (ONPG) hydrolysis assay for testing the permeability of the planktonic bacterial membrane. F) Illustrative scheme of thermotherapy NTP. G) In vivo temperature variations and thermal images in 10 min. Obtained photographs from the infection model of mouse subcutaneous implant. Red circles show infection areas. Abbreviation, HF: hydrofluoric acid, TPAOH: tetrapropylammonium hydroxide, APTES: 3-aminopropyltriethoxysilane, TP: titanium plate, NIR: near-infrared. Reproduced with permission. [43] Copyright 2021, American Chemical Society.
Table 2. MXene-integrated nanocomposites for cancer therapy.

<table>
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<tr>
<th>Formulation</th>
<th>Cancer</th>
<th>Combined therapy</th>
<th>Main achievements and therapeutic performance</th>
<th>Refs.</th>
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| Ti3C2−polyvinyl pyrrolidone@doxorubicin jade | Colorectal carcinoma | Iron chelation/chemotherapy/PTT | – The apoptotic cell death has occurred, and the iron depletion–induced iron transferrin receptor (TfR) was downregulated.  
– The tumor growth inhibition effect was observed. | [113] |
| Carbon dot@Ti3C2/Ta heterojunctions | Breast            | SDT/PTT                       | – The photothermal conversion efficiency in the NIR-II bio-window was enhanced by 64.5%.                        | [114] |
| The assembly of Nb2C plasmon (MXene), Pt nanozymes, and DOX | Cervical carcinoma | Chemotherapy/PTT              | – The blood perfusion and drug extravasation were enhanced due to the dilating tumor vessels by the excellent photothermal properties of the composite.  
– The activity of the nanozyme was improved due to the thermoplasmic effect.  
– The reversed multidrug resistance could be achieved by downregulating HIF-1α and reducing the mitochondrial energy supply for P-glycoprotein due to the more generation of O2 and ROS through NIR-II laser irradiation. | [115] |
| Ti3C2@chitosan–MnFe2O4 (TC@Ch–MFO) | Pancreatic        | CDT/PTT/magnetic resonance imaging | – The tumors were effectively inactivated due to the excellent photothermal and CDT efficacy, attributing the ROS-evolving of TC@Ch-MFO.  
– TC@Ch-MFO served as a T1 and T2 dual-responding MRI contrast agent.  
– The negligible toxicity against the normal tissue cells was observed. | [116] |
| Hydroxyapatite/chitosan/hyaluronic acid/ MXene/gold nanorods | Breast            | Chemotherapy/PTT              | – The superior pH/NIR dual-responsive drug delivery characteristics were exhibited.                       | [117] |
| MXene@hydrogel                  | Melanoma          | Chemotherapy/PTT              | – The high photothermal conversion efficiency, as well as good photothermal stability, was exhibited.  
– The on/off switch control for drug release could be achieved due to the reversible softening/gelling of MXene@hydrogel, thus, the blood drug concentration would be maintained effectively in clinical treatment. | [118] |
| MXene@agarose/TNF-α             | Colorectal carcinoma | Chemotherapy/PTT             | – MXene@hydrogel/ protein system enabled the “on/off”, controlled drug release and multichannel tuning of the release rate.  
– The programmed cell deaths (PCD) of tumor spheroids were induced by an NIR light due to the promoting proapoptotic signaling pathway by the integrated TNF-α. | [119] |


The MnO2/TaC3-SP (soybean phospholipid) nanosheets served as high-performance contrast agents for simultaneous CT (due to the tantalum component), photoacoustic imaging (due to the nanocomposite's photothermal-conversion property), and tumor microenvironment-responsive T1-weighted MRI (due to Mn2+ release from the MnO2 component), as shown in Figure 8C–E. In the in vivo assessment, the MnO2/TaC3-SP + NIR group demonstrated more powerful tumor growth suppression than the other groups, indicating that light-triggered PTT was superior in the cancer ablation investigation (Figure 8D–G).[22] In addition, the SP surface modifier guaranteed high stability of the Ta-based MXenes in physiological conditions.[12]

The nanosonosensitizer-augmented PDT could combine with PTT to realize high tumor-therapeutic efficacy. These therapeutic modalities could be rationally combined to achieve improved therapeutic outcomes.[85,112] In a study, Ti3C2/g-C3N4 nanocomposites were developed to combine PTT and in situ oxygen-generating enhanced PDT.[103] The integration of Ti3C2 to g-C3N4 might significantly increase g-C3N4 absorption in the NIR region and subsequently increase the photocatalytic activity of the resultant nanocomposites to create more ROS. After further modifying triphenylphosphonium bromide on Ti3C2@g-C3N4 (Ti3C2@g-C3N4−TPP), an ROS-augmented and mitochondria-targeted nanomedicine was developed to combat cancer in conjunction with PTT (Figure 9A,B).[103] As shown in Figure 9C, the synergistic type I and type II PDT could realize under NIR irradiation. In the type II PDT and under the light illumination, abundant O2 could be produced via splitting endogenous water by Ti3C2@g-C3N4 NPs. Therefore, the generation of cytotoxic 1O2 through energy transfer to O2 is subsequently started. Through the type I PDT, the electrons in the valence band (VB) of g-C3N4 excited their conduction band (CB) to generate photoactivated electrons and holes.[103] The excited holes reacted with water molecules and thus generated ‘OH species. Moreover, due to the Schottky junction between Ti3C2 and g-C3N4, the excited electrons of g-C3N4 could transfer to Ti3C2, thus further generating O2− as a potent ROS via reduction of O2. Electron spin resonance spectra of g-C3N4 and Ti3C2@g-C3N4 (670 nm laser, 0.48 W cm−2) confirmed the type of generated ROS, i.e., ‘OH, O2−, and O2. A good photothermal effect of Ti3C2@g-C3N4 nanocomposites at different concentrations was observed under 808 nm laser irradiation (Figure 9D).[103] In the in vitro studies, compared to the pure Ti3C2 nanosheets, the zeta potential of Ti3C2@g-C3N4 nanocomposite increased from −4.5 to −22.4 mV. Additionally, subsequent surface...
modification by TPP and PEGNH₂ further increased the zeta potential to 7.6 and −3.0 mV, respectively. This achievement conferred the nanocomposites good physiological stability in PBS (pH = 7.4, 10 mM), FBS and Dulbecco’s modified Eagle’s medium (DMEM), which are crucial factors for in vivo applications. The in vivo multimode PTT and PDT on the tumor-bearing nude mice showed that the Ti₃C₂/g-C₃N₄-TPP nanocomposites exhibited powerful anticancer efficacy (Figure 9E). No abnormality in standard blood biochemical indexes was detected in the Ti₃C₂/g-C₃N₄-TPP-treated group, indicating no significant renal and hepatic cytotoxicity of the composite. Additionally, after intravenous injection of the nanosheets for two weeks, the H&E staining assay of the major organs including liver, kidney, lung, heart, and spleen no significant inflammation and chronic

Figure 8. Design, preparation, characterization, and application of MnOₓ/Ta₄C₃-SP nanocomposites sheets for in vitro and in vivo photothermal hyperthermia of cancer. A) Schematic illustration of the synthetic procedure of MnOₓ/Ta₄C₃-SP nanocomposite. B) TEM images of MnOₓ/Ta₄C₃ nanosheets. C) In vivo 3D reconstruction CT images of mice before and after i.v. administration MnOₓ/Ta₄C₃-SP nanosheets. D) PA signal values, and E) MRI-signal intensity of 4T1 tumor-bearing mice after i.v. administration of the nanocomposites for prolonged time intervals. F) IR thermal elevated temperature curves at the tumor sites of 4T1 tumor-bearing nude mice using two types of treatments under 808 nm laser irradiation. G) Relative tumor volume variations after disparate injections. Reproduced with permission.[22] Copyright 2017, American Chemical Society.
pathological toxicity was observed. Such findings confirmed the good biocompatibility of Ti$_3$C$_2$/g-C$_3$N$_4$-TPP nanocomposites.

As we mentioned above, the functionalization of MXenes can bestow to tune physiochemical properties to realize specific biomedical requirements. For instance, superparamagnetic iron oxide nanoparticles (IONPs) were in situ grown onto the surface of Ta$_4$C$_3$ MXene fabricated by exfoliation strategy. Ta$_4$C$_3$–IONP nanocomposite was further functionalized by soybean...
phospholipid (referred to as Ta_{4}C_{3}–IONP–SP), endowing the nanocomposites with great physiological stability (Figure 10).[15] Soybean phospholipid as surface modifier endowed the Ta_{4}C_{3}–IONP–SP composites with high stability and dispersibility in various physiological media, including PBS, DMEM, and saline solution as well as simulated body fluid. Ta element has a high atomic number (73) and high X-ray attenuation coefficient. Furthermore, the IONPs onto the surface of Ta_{4}C_{3} nanosheets endowed the Ta_{4}C_{3}–IONP–SP nanocomposites with contrast-enhanced T2-weighted MR imaging. In addition, Ta_{4}C_{3} as a member of the 2D MXenes family, exhibited high photothermal conversion efficiency. Collectively, such intrinsic properties of Ta_{4}C_{3}–IONP–SP NCs successfully exploited in the concurrent CT/MR dual-modality imaging-guided PTT of breast cancer without reoccurrence (Figure 10A).[15] Additionally, after one month of intravenous treatment, no evident loss of body weight or accidental death, as well as no abnormalities in blood index variables, were seen in mice treated with Ta_{4}C_{3}–IONP–SPs. These results suggested that the nanocomposite nanosheets had favorable biocompatibility, making them useful in clinical translation, particularly for future imaging-guided PTT of breast tumors.

The majority of previous studies on the biomedical application of MXene mainly focused on PTT in the NIR-I window. Such a window suffers from a limited penetration depth.[85] The NIR-II window (1000–1500 nm) induced PTT has been used to realize a deeper penetration and better tumor ablation property to address this problem.[92] In a study,
Ti$_3$C$_2$@Au nanocomposites were constructed by Au NPs growth on the surface of the Ti$_3$C$_2$ nanosheets, which greatly improved the biocompatibility of the nanocomposites (Figure 10B). Such stability and enhanced biocompatibility were attributed to the thiol group of the Au NPs. Importantly, this type of modification endowed the nanocomposites with high absorbance in the NIR-II window and high X-ray attenuation abilities, which were successfully utilized for PA/CT dual-modal imaging of cancer (Figure 10B). Furthermore, the mild photothermal effect of the Au-modified MXene improved tumor oxygenation, thus significantly enhancing radiotherapy (RT). In vivo study, tumor growth inhibition was realized clearly through the Ti$_3$C$_2$@Au injection under X-ray irradiation and 1064 nm laser illumination, demonstrating the synergistic therapeutic effect of the multifunctional NCs. Interestingly, after the various treatments for a month postinjection, no noticeable weight loss and abnormality in the major organs was observed, thus indicating the biosafety of the nanocomposites for in vivo application. These exciting results open a new avenue in the pursuit of developing multifunctional MXene-based nanocomposites for cancer diagnosis with minimal adverse effects.

PTT-triggered sequential catalytic nanomedicine on the surface of the 2D MXene matrix was introduced (Figure 10C). In the tumor microenvironment, the loaded glucose oxidase could catalyze the tumor-overtaken glucose to produce H$_2$O$_2$. These in situ made products, in combination with endogenous H$_2$O$_2$, were transformed to hydroxyl radicals by the subsequent catalyst, i.e., coloaded iron oxide nanoparticles, to destroy cancer cells successfully (Figure 10C). Importantly, these cascade reactions were further speeded up by the elevated local heat generated by the MXene matrix under NIR light irradiation, thus achieving a high synergistic cancer-therapeutic outcome. Performance of the intriguing MXene-based composite systematically proved both in vitro and in vivo levels. Therefore, this work noticeably broadened the biomedical applications of 2D MXenes and the concept of “nanodynamic therapy.”

In another study, Li and co-workers introduced a micellar hydrogel for the combined loading of Ti$_3$C$_2$ (NIR-II triggered photothermal absorbing agent) and Combretastatin A-4 (CA4) (vascular disrupting agent) to achieve synergistic therapy of solid tumors (Figure 11A). The triblock PDLLA–PEG–PDLLA copolymer was dissolved in DI water to form PLEL micelles by the self-assembly of the copolymer. Next, CA4 was dissolved into PLEL micellar solution to allow the incorporation of the hydrophobic drug into the hydrophobic core of the copolymer micelle to improve the solubility of the drug while the loading efficiency was about 99.6%. Through dispersing the Ti$_3$C$_2$ nanosheets, which were harvested by acid/alkaline etching method, in the CA4@copolymer micelle solution, the Ti$_3$C$_2$/CA4@copolymer micelles were obtained. The synthesized micellar hydrogel could be converted from sol to gel at the body temperature and showed good photothermal efficiency of 41.4% with a laser power of 1 W cm$^{-2}$. The PTT effect was attributed to the ultrathin MXene structure and thermotherapy. The hydrogel was assessed in the mice bearing 4T1 tumors. After irradiation using a 1064 nm NIR laser (1.0 W cm$^{-2}$), the tumor temperature was increased to 51.3 °C within 5 min. This temperature can cause irreversible damage to the target cells. To assess the photothermal activity of Ti$_3$C$_2$ nanosheets, the Live/Dead staining method was utilized (Figure 11B) using Calcein-AM and PI with green and red fluorescence, respectively. When 4T1 cells were incubated with Ti$_3$C$_2$ and exposed to the 1064 nm irradiation, approximately all cells were killed, whereas other groups did not show remarkable cell death. It was shown that free CA4 has fast clearance and undesirable distribution in the biological environment. However, its encapsulation into the hydrogel improved its cellular uptake. As shown in Figure 11C, the cellular internalization of the micelles was increased over-time when the fluorescent molecule, Cy5 was encapsulated within them. Furthermore, the in vivo antitumor efficiency was evaluated on the mice bearing 4T1 tumors with an initial volume of 200 mm$^3$. The CA4@copolymermicellar hydrogel, due to sustained drug release and enhanced retention, had a better antitumor effect than the free drug. The apoptosis/necrosis of 4T1 cancer cells showed that after five days from the beginning of the therapy, higher apoptosis occurred in the group Ti$_3$C$_2$/CA4@PLEL hydrogel + NIR compared to other treatment groups. Angiogenesis was also monitored by CD31 staining. The results demonstrated a reduced number of vessels in the groups that received CA4 compared to those without CA4 (Figure 11D). Overall, this research found that combining PTT with vascular disruption had a synergistic impact on tumor elimination.

For effective treatment of cancer, PTT can be combined with different therapeutic strategies like photodynamic therapy,[121] radiotherapy,[122] immunotherapy,[123] chemotherapy,[124] etc. For instance, Zhang and co-workers fabricated DOX-loaded cellulose/Ti$_3$C$_2$ MXene composite hydrogels. They showed that this dual-modality photothermal/chemotherapy system offered desirable biocompatibility, excellent photothermal property, and high loading capacity of DOX.[125] In addition, they demonstrated the release of the drug was triggered by the photothermal effect and could effectively kill tumor cells while preventing their recurrence. Recently, Deng and co-workers proposed a novel multifunctional hydrogel that consists of tobramycin (TOB), sulfonated polyetheretherketone (SP), Ti$_3$C$_2$ nanosheets, and gelatin methacrylate (GelMA), called SP@MX-TOB/GelMA.[126] In this study, the implant could effectively kill osteosarcoma cells because of its potential photothermal property. The hydrogel could also kill *E. coli* and *S. aureus* bacteria due to the delivery of TOB. Additionally, the material displayed biocompatibility, the osteogenic activity of preosteoblasts, and favorable osseointegration on the implant.

For bone cancer treatment, destructive surgeries such as limb-salvage surgery and amputation followed by chemotherapy are the common strategies of surgeons.[127] Regrettably, unsuccessful resection and inevitable local recurrence were commonly determined after these massive treatments. This limitation is mostly due to tumor anatomical complexity and the invasive nature of cancer cells. Aside from poor life quality and severe cardiac toxicity, the possible surgical bone defects can disrupt tissue’s self-healing ability and bring long-term pain to patients.[128,129] To avoid surgery and its massive side effects, it is an urgent priority to design and construct biomaterials with multiple functionalities integrating eradication of recalcitrant tumors and bone tissue reconstruction at the same time. Accordingly, these biomaterials should carry and release chemotherapy
agents and degrade into products with an accelerating effect on the tissue remodeling and so healing process.\textsuperscript{[130,131]}

Aside from their versatile applications of MXene nanosheets in energy storage,\textsuperscript{[132]} water purification,\textsuperscript{[68]} and catalysis,\textsuperscript{[133]} their applications have been recently extended to biomedical studies, such as biosensing,\textsuperscript{[134]} PTT,\textsuperscript{[135]} infection treatment,\textsuperscript{[90]} and intracellular fluorescent imaging. The MXenes’ captivating performance in biomedical fields has captured the attention of tissue engineers. Ti\textsubscript{3}C\textsubscript{2} MXene nanosheets with high biocompatibility possess efficient photothermal conversion in the NIR region.\textsuperscript{[136]} For example, the Ti\textsubscript{3}C\textsubscript{2} MXenes were integrated into the 3D-printed bioactive glass scaffolds (TBGS) to construct the biomaterials with multiple functionalities for simultaneous eradication of bone cancer cells along with regeneration of bone tissue (Figure 12A,B,D).\textsuperscript{[70]} First, such a platform could eradicate the bone cancer cells due to their photothermal property by applying NIR laser (808 nm) irradiation (Figure 12C). Second, the bioactive glass with a 3D interconnected structure assisted the hBMSCs differentiated into osteoblasts.\textsuperscript{[137]} Third, the produced Ti-based species through the biodegradation of Ti\textsubscript{3}C\textsubscript{2} MXenes could accelerate new bone formation.\textsuperscript{[138]} Moreover, the bioactive glass-based materials biodegraded gradually into the bioactive minerals (e.g., Ca\textsuperscript{2+} and PO\textsubscript{4}\textsuperscript{3-}), providing newly constructed bone tissue. The TBGS scaffold was implanted into the bone defect site to eradicate residual cancerous cells and contribute to bone repair. The obtained microcomputed tomography (micro-CT) from the back and the front surface of a cranium at week 24 after implantation showed that the TBGS had a better regeneration effect for bone defects in comparison with the MXene-free bioactive glass (BGS) (Figure 12G).
Figure 12. A) Designed and fabricated Ti$_3$C$_2$ MXene-integrated bioactive glass scaffold (TBGS) targeted for bone cancer ablation and regeneration of bone tissue. I) Fabrication procedure of TBGS, including 3D printing of pure bioactive glass scaffold (BGS), integration of Ti$_3$C$_2$ MXenes, and biodegradation of Ti$_3$C$_2$ MXenes on BGS. II,III) TBGS was used for the eradication of osteosarcoma cells through photothermal therapy both in vitro (II) and in vivo (III). IV) Bone tissue regeneration after implantation of TBGS and BGS. B) Illustrative scheme of cancerous cell elimination by Ti$_3$C$_2$ nanosheets existing on TBGS. C) Relative cell viability of bone tumor cells (Saos-2) after treatment under different conditions. The “200 µL” and “Dry” groups mean TBGS + NIR group in 200 µL Dulbecco’s modified Eagle’s medium (DMEM) and dry environment (removal of all DMEM), respectively. The other groups were performed in 400 µL DMEM. D) Photographs and SEM images of pure BGS and TBGS: pure BGS (c1, c2) and TBGS (d1, d2). Scale bar for photographs: 3 mm and for SEM: 500 µm. E) Human bone marrow mesenchymal stem cells (hBMSCs) proliferation as measured by a standard CCK-8 assay; n = 3. F) Alizarin red S-stained mineralized calcium deposited during osteogenic differentiation for control, BGS, and TBGS at day 21. The abundance of red calcium nodules in the TBGS indicates in vitro osteogenic capability of hBMSCs. G) In vivo osteogenesis efficiency of BGS and TBGS. (I,II) 3D reconstructed circular cranial bone defects at the 24th week after scaffolds implantation. (III–VI) Microcomputed tomography (micro-CT) images of cranial defect areas with a diameter of 5 mm at week 24th postoperation. VII) Volume percentage of newborn osseous tissue to entire defect volume (BV/TV) (n = 6). (VIII, XI) Value of bone mineral density (BMD) and a total of porosity (TOT) in newborn osseous tissue (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001. Reproduced with permission.[70] Copyright 2020, Wiley-VCH.
Moreover, this tissue regeneration was followed by the quantitative parameters obtained from histomorphometric micro-CT. The volume percentage of newborn osseous tissue to entire defect volume (BV/TV) for TBGS was higher than BGS. Additionally, the higher bone mineral density (BMD) value and lower total porosity were obtained for TBGS in comparison with BGS, revealing the outstanding osteogenic efficiency of TBGS (Figure 12G (VII–IX)).[70]

It has been shown that nitric oxide (NO), as an endogenous and essential biological molecule, regulates various biological mechanisms, such as skeletal mechanotransduction, immune responses, cardiovascular system modulation, and neuronal communication.[139,140] Its potential application has been successfully exploited in antibacterial, wound healing, angiogenesis, and stem cell therapy.[141–143] In a study, It was shown that the NO concentration between $1 \times 10^{-6}$ to $1 \times 10^{-3}$ m had a direct anticaner effect. By contrast, low NO concentrations ($<10^{-9}$ m) regulated endothelial cell proliferation and migration as well as stimulated vascular remodeling and angiogenesis.[144,145] By inspiring these features of NO, Yang et al. designed and constructed a multifunctional scaffold targeted for bone tumor killing and tissue engineering simultaneously (Figure 13A,B).[42] They prepared 3D-printed bioactive glass scaffolds with large macropores containing 2D niobium carbide (Nb2C) MXenes wrapped with 5-nitosothil (NO donor)-grafted mesoporous silica—the so-called MS/MXene-SNO. Furthermore, the multifunctional biomaterials exhibited anticaner effects due to the induced photonic hyperthermia caused by the photothermal conversion capacity of Nb2C MXenes. They showed NO release in high concentration, a process known as gas therapy (Figure 13C). In the later stage, the released NO in low concentration improved angiogenesis and regeneration of bone tissues based on the 3D printed scaffold. As a consequence of biodegradation, the calcium- and phosphorous-released bioactive glass scaffold promoted bone tissue remodeling. Moreover, the angiogenesis effect of in situ released NO could also promote tissue remodeling.

In line with this, in a recent study, 2D Nb2C MXene nanosheets were successfully incorporated into a 3D printed bioactive glass scaffold (NBGS) for osteosarcoma treatment (Figure 13A).[25] Due to the photonic response of Nb2C nanosheets in the NIR-II biowindow, the NBGS exhibited a specific capability of bone cancerous cell ablation and promotion of angiogenesis to accelerate bone defect regeneration (Figure 14B). The biodegradation of MXene nanosheets could promote blood vessels' migration and neogenesis. Therefore, they could transport vitamins, oxygen, energy, and immune cells in the bone defect sites to accelerate NBGS biodegradation. The NBGS biodegradation has demonstrated its ability to stimulate bone tissue formation. The ions released (i.e., Ca$^{2+}$ and PO$_4^{3-}$) from the NBGS can effectively promote bone tissue mineralization (Figure 14D). Furthermore, the implanted NBGS could penetrate tissue depth during NIR-II-induced hyperthermia and significantly kill osteosarcoma cells. This feature led to the lifespan prolongation of tumor-bearing mice. The NBGS displayed biocompatible, osteoconductive, osteoinductive, and proangiogenic in vivo experiments (Figure 14C,D), making it a unique implantable biomaterial for the treatment of bone malignancies.

### 6. Biosensors and Wearable Electronics

MXene-based components have been used actively or passively as redox transducers and electrocatalysts for biomarkers, identifying nanoparticles, prescription products, and environmental toxins.[146] The major reason for broadening the MXenes domain in the sensor area is straightly related to their changeable/easy surface functionalization and chemical features.[147] Considering the mentioned advantages, MXenes have emerged in the wide world of sensors, including gas/humidity sensors, optical/electrochemical sensors, and stress/strain sensors.

For instance, Ti$_3$C$_2$Tx exhibited a broad optical absorption region from visible to near-infrared, resulting in high photothermal yields. The electron of gas molecules could also adsorb on the defect sites and/or surface terminations of MXene nanosheets, leading to resistance increases.[146] Another research reported MXene-based sensing, denoted as titanium carbide-based, as a chronoamperometric biosensor. The pristine MXene was a transducer platform for glucose sensing with high electrocatalytic activity, selectivity, and extensive linear ranges (50–750 μM).[148]

MXenes possess van der Waals interactions between adjacent sheets, resulting in the thin interlayer distance and significant aggregation, limiting their feasible usage.[149–151] Hence, improving the features of MXenes could be achieved by widening the interlayer space to get greater surface area, further active sites, and broader ionic transportation channels.[152] To this end, the design or fabrication of MXenes-based composites can enhance complementary/synergistic effects on efficiency.

With the growing human need for new diagnostic methods, easy-to-use and decentralized biosensors have been emerged. As a model, glucose sensors can be necessary for patients and pharmaceutical companies to provide an effective diagnostic technology. Personal biosensor-based diagnostic devices enable patients or healthy individuals to monitor the disease, early diagnose, or ensure that a person’s health is stable.[153] Gaining in-depth insights into the science of materials and the biological behavior of MXene nanosheets and their composites can offer a wide range of promising applications with the potential for clinical translation into human health.[154] MXenes’ favorable properties, including their peculiar shape, unique surface chemistry, endearing conductivity, and biocompatibility, make them an excellent platform for developing novel electrochemical sensing and biosensing devices.[155,156] In this section, some various MXene-integrated biosensors were summarized in Table 3.

Although MXene-based composites exhibit significant potential in the field of biomedicine as a biosensor, in the optics domain, they possess poor luminosity. To increase the efficiency of MXene in the photoluminescence features, they have been combined with quantum dots or fluorescent dyes.[157] The sensing performance of phospholipase D has been studied by MXenes’ composite. Some dyes, such as rhodamine B possess natural fluorescence properties; hence their optical features could be transferred to MXenes when prepared as a composite. The surface of Ti$_3$C$_2$ MXene was changed with rhodamine B, and the dye’s inherent fluorescence was quenched. By contrast, in the presence of phospholipase D, the dye got away from MXene nanosheets, and therefore, fluorescence restoration accrued.
Figure 13. A) Illustrative scheme of the multifunctional therapeutic platform. The designed 3D-printed scaffolds were targeted for induced photonic hyperthermia for ablation of bone cancer cells and controllable NO release (gas therapy) for bone tumor eradication and tissue regeneration simultaneously. B) Schematic illustration of MBS scaffolds for in vivo bone tumor eradication. C) IR thermal images of tumor lesions under different applied conditions (BGS + NIR, NBGS + NIR, and MBS + NIR). Abbreviation: BGS: bioactive glass scaffold, NBGS: integrated BGS with Nb$_2$C MXene nanosheets, MBS: integrated BGS with Nb$_2$C MXene nanosheets wrapped with S-nitrosothiol-grafted mesoporous silica, NIR-II: second biowindow of near-infrared. Reproduced with permission.[42] Copyright 2020, Wiley-VCH.
This sensing route can be introduced as a novel fluorescent probe for imaging phospholipase D. According to the National Cancer Institute, biomarkers are biological molecules existing in blood, fluids, and tissues that can be identified as normal/abnormal biological conditions or pathogenic circumstances/diseases.
Table 3: Summary of MXene-integrated biosensors.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Analyte</th>
<th>Sensing range</th>
<th>Limit of detection (LOD)</th>
<th>Main achievements/diagnostics performance</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prussian blue/Ti3C2 MXene</td>
<td>Exosomes</td>
<td>5 × 10^2–5 × 10^3 particles µL^-1</td>
<td>229 particles µL^-1</td>
<td>Detection of exosomes secreted by various cancer cells (i.e., the breast cancer cell line (BT474 cells), cervical cancer cell line (Hela cells), and human ovarian cancer line (OVCAR cells)) with high specificity in serum samples was performed.</td>
<td>[157]</td>
</tr>
<tr>
<td>MXene–MoS2</td>
<td>MicroRNA-21</td>
<td>100 fm to 100 nm</td>
<td>26 fm</td>
<td>Satisfactory selectivity, reproducibility, and stability were achieved by the MXene-integrated biosensors.</td>
<td>[158]</td>
</tr>
<tr>
<td>Ti3C2–MoS2 MXene</td>
<td>Toxic gases</td>
<td>10–100 ppm</td>
<td>N.R. a)</td>
<td>The composite showed reaction signals to some hazardous gases (i.e., NO2 ammonia and methane) and suggested multigas-detecting sensors that are very sensitive in the air (at room temperature).</td>
<td>[159]</td>
</tr>
<tr>
<td>MXene–Au</td>
<td>Gram-negative and Gram-positive bacteria</td>
<td>3 × 10^3–3 × 10^6 CFU mL^-1</td>
<td>3 × 10^3 CFU mL^-1</td>
<td>This nanocomposite could detect bacteria sensitively and showed antibacterial and photothermal sterilization effects.</td>
<td>[160]</td>
</tr>
<tr>
<td>Ti3C2T, MXene–Au NPs@ polyimide thin film</td>
<td>Carcinoembryonic antigen</td>
<td>0.1–100 ng mL^-1</td>
<td>0.001 ng mL^-1</td>
<td>The biosensor illustrated high selectivity compared with other common tumor markers. Clinical serum samples had successful results compared with values obtained through the ELISA method.</td>
<td>[146]</td>
</tr>
<tr>
<td>MXene N-Ti3C2 quantum dot/Fe15</td>
<td>Glutathione</td>
<td>0.5–100 µm</td>
<td>0.17 µm</td>
<td>It could be considered a promising probe for detecting/showing cellular imaging of glutathione in MCF-7 cells. It might provide a new way for imaging-guided precision cancer diagnosis.</td>
<td>[161]</td>
</tr>
<tr>
<td>MXene-based cytosensor dot/Au</td>
<td>HER2-positive cancer cells</td>
<td>102–106 cells mL^-1</td>
<td>47 cells mL^-1</td>
<td>The MXene-based cytosensor might be extended for detecting other tumor cells and used in targeted drug delivery.</td>
<td>[162]</td>
</tr>
<tr>
<td>MXene-derived quantum dot/Au</td>
<td>Triple-negative breast cancer</td>
<td>5 fm to 10 µm,</td>
<td>1.7 fm</td>
<td>It could be applied as an idea for the green synthesis of MXene and a guide for applying MQD@Au NBs heterostructure in the field of electrochemiluminescence sensing.</td>
<td>[163]</td>
</tr>
<tr>
<td>MXene @Au NPs@ methylene blue</td>
<td>Prostate-specific antigen</td>
<td>5 pg mL^-1 to 10 ng mL^-1</td>
<td>0.83 pg mL^-1</td>
<td>This biosensing system has been proved to be a universal anti-fouling detection strategy by changing the recognition sequence of the peptides. It could be combined with various functional peptides to construct different ratiometric anti-fouling electrochemical biosensors.</td>
<td>[164]</td>
</tr>
<tr>
<td>Ti3C2@ReS2</td>
<td>Cancer-related miRNA-141</td>
<td>0.1 fm to 1 nm</td>
<td>2.4 am</td>
<td>It proved a promising potential of ReS2 for photoelectrochemical bioanalysis and also a novel and efficient avenue by using Ti3C2–based semiconductors to boost the charge separation efficiency.</td>
<td>[165]</td>
</tr>
</tbody>
</table>

a) Not reported.

Recently, electronic flexible/stretchable sensors have opened up new opportunities for novel applications.\[^{168,169}\] These wearable sensors can indicate promising applications in intelligent medical diagnostics and humanoids.\[^{170–172}\] They can be applicable in real-life conditions due to getting electricity from mechanical stimuli and the subsequent generation of electrical sensing signals.\[^{173,174}\] The outstanding properties of MXenes have turned them into widely used nanofillers into polymer matrices for the construction of flexible, stretchable, and deformable electronics. For instance, a self-powered e-skin sensor was prepared by loading MXene (Ti3C2T) nanosheets into glycerin/poly(dimethylsiloxane) film. This e-skin sensor could be attached to the skin and monitor the temperature changes ranging from 15 to 25 °C with satisfactory sensitivity.\[^{175}\]

The electrochemical biosensor possesses a significant performance in providing figures of merit depending on the amount of catalytic activity of the substrate, the specific surface area, the ability of charge transfer, and conductivity. MXenes’ excellent catalytic efficiency and broad surface area enabled increased aptamer loading for exosome capture, creating the electrochemiluminescence signal (Figure 15A).\[^{176}\] Polymer-functionalized MXene composites could also be a good candidate for electrochemical biosensors (Figure 15B). For example, a modified glassy carbon electrode (GCE) via Ti3C2T MXene–chitosan nanocomposite was fabricated as a platform for sarcosine oxidase (SOx) stabilization and sensitive sarcosine detection in urine samples.\[^{176}\] It showed a low detection limit of 18 nm in a linear range of 78 µM. The biosensors worked based on hydrogen peroxide electrochemical reduction. The developed biosensor provided a short response time of 2 s and a high recovery index of 102.6% to detect sarcosine in a urine sample.\[^{176}\]

Metalloenzymes inherently produce low electrochemical signals and possess low stability. MXenes have made it possible to obtain great sensitivity and selectivity by overcoming their limits.\[^{178}\] A glucose biosensor has been proposed as one of the most common enzymatic-based electrochemical biosensors in that the glucose oxidase enzyme was used to detect...
glucose. The Au/MXene nanocomposite has been fabricated via the selective etching of Al from the Ti₃AlC₂ MAX phase to produce Ti₃C₂Tx MXene nanosheets. Moreover, a chemical reduction procedure was used to create the anchored Au NPs on the surface of the MXene sheets. MXene nanosheets forgave high conductivity through an enzyme immobilization matrix. Moreover, Au–MXene nanocomposite could improve the electron transfer kinetics between the electroactive center centers of the enzyme. Graphene oxidase (GOx) as an enzyme could also be applied for glucose sensing via immobilization on the MXene/GCE. Nafion was implemented to both eliminate the interfering signals and increase the adhesion between enzymes and the GCE (Figure 16A). MXenes with a high surface area lead to charge storage, thus magnifying the sensitivity and/or linear range. A complementary DNA-ferroocene-MXene probe was employed in a developed biosensor to amplify the breast cancer biomarker/Mucin 1 signal. The MXene nanosheets could be acted as a nanocarrier complementary DNA ferroocene due to their high surface area and active sites for binding. The biomarker competed with the MXene-based probe for binding on the modified-electrode surface. Hence, a DNA conformational change occurred. This conformational change resulted in the dissociation of the aptamer and complementary DNA-ferroocene and the separation of the MXene-based probe from the electrode fabrication. Finally, the current signal was decreased.

MXenes composites were also used for disease prediction/diagnosis, specifically cancer treatments. For instance, Cy3 labeled CD63 aptamer-Ti₃C₂Tx MXenes nanocomposite was created as a nanoprobe for biomarkers (Exosomes) sensing. While the aptamer was preferentially adsorbed on the MXene nanosheets by hydrogen bonding, the aptamer and MXenes interacted via metallic chelation. The sensing mechanism was based on a ratiometric fluorescence resonance energy transfer between aptamer and MXenes. As a result of this phenomenon, the fluorescence of Cy3-CD63 aptamer was quenched quickly and restored remarkably after exosome–aptamer interaction and release from the MXenes surface (Figure 16B).

One study used an in situ coprecipitation approach to create layered double hydroxide nanoflakes based on MXene-NiFe (Figure 16C). The functional groups of MXene induced negative surface charges to facilitate the loading/nucleation of the layered double hydroxide nanoflakes. The composites served as a nanocatalyst which catalyzed H₂O₂-decomposition and hydroxyl radicals’ generation. The authors managed to use this system to detect glutathione by exerting a catalytic impact on colorimetric detections in the presence of tetramethylbenzidine. 
Figure 16. A) The working mechanism of an enzymatic biosensor for glucose determination. Reproduced with permission.\textsuperscript{[14]} Copyright 2019, Elsevier Ltd and Techna Group S.r.l. B) Graphical illustration for biomarker sensing; Cy3-CD63 aptamer was mixed with MXenes nanosheets (Off-fluorescence mode). Then, in the presence of exosomes, the aptamer interacted with the biomarker of exosomes, and the fluorescence mode appeared. Reproduced with permission.\textsuperscript{[181]} Copyright 2018, American Chemical Society. C) Schematic illustration of MXene nanosheet and the Ni, Fe layered double hydroxide as MXene-based composite for glutathione diagnosis. Reproduced with permission.\textsuperscript{[179]} Copyright 2019, American Chemical Society.
The function of the colorimetric sensor was such a way that TMB was oxidized in the presence of hydrogen peroxide and produced blue color at the same time. This color gradually faded in the presence of glutathione and MXenes-based nano-hybrid as a catalyst (Figure 16C).

MXene can easily be combined with DNA via strong chelation interaction between Ti and DNA phosphate groups and introduce a variety of diagnostic composites. For instance, Ti$_3$C$_2$T$_x$ nanosheets could be modified by DNA nanostructure to introduce an electrochemical MXene/DNA biosensor for detecting gliotoxin. In this context, tetrahedral DNA nanostructures have interacted with MXene nanosheets through their phosphate groups. In fact, the MXene nanosheets accelerated the electron transfer between electrochemical species and the underlying electrode surface. The sensing signal has produced through the changing configuration of TDN after binding to target molecules. The electrochemical signal of this biosensor was monitored via the current as an output response for gliotoxin detection. The current was enhanced as the gliotoxin concentration increased (detection range: 5 pm–10 nm; limit of detection: 5 pm). Such biosensors could be expanded to detect other mycotoxins as well (Figure 17A,B).

Wearable electrochemical biosensors can provide the user with sweat-based analysis from the metabolic feedback. Wearable electrochemical biosensors as noninvasive monitoring devices for sweat-based analysis are still suffering from some challenges, such as instability of enzymes/biomaterials with frequent examinations, narrow detection range and sensitivity, and low durability. Using MXene-based composites such limitations have been partially solved. For instance, composite...
MXene and Prussian blue was applied for biomarker sensing in sweat. These flexible and wearable composites were capable of detecting certain biomarkers in sweat, such as glucose and lactate. The designed electrochemical biosensor was based on sensing working electrodes, including MXene nanosheet and Prussian blue composite on a hydrophobic substrate with a solid/liquid/air interface. A superhydrophobic carbon fiber (as a three-phase interface) provided excellent performance and stability by protecting the internal connector of the sensor from corrosion. This electrochemical biosensor illustrated high sensitivities of 35.3 and 11.4 µA mm⁻¹ cm⁻² for glucose and lactate, respectively. Its physiochemistry signals were simultaneously measured for glucose and lactate sensing with high repeatability (Figure 17C,E).[183]

Another interesting case reported for MXene-based sensors is their use in diagnosing dental disease. For instance, a bioaerogel and 3D porous cellulose/Ti₃C₂Tex MXene array was developed as a sensor for the diagnosis of periodontal diseases. The biosensor was flexible and had excellent mechanical qualities due to the presence of the integrated MXene nanosheet. Additionally, the system was pressure and ammonia gas-sensitive, making it a viable sensor for diagnosing and monitoring oral health. It is worth mentioning that the sensor was biodegradable, biocompatible, and decomposed in very low H₂O₂ concentrations (Figure 18).[184] Bacterial cellulose/Ti₃C₂Tex MXene (BC/MXene) aerogels were flexible and easily degraded. This sensing platform was provided to prevent dental diseases by identifying the occlusal force and local diffusion.
of NH$_3$ molecules. This device was not only highly sensitive to occlusal force but also differentiated the order of contact by specifying contact locations. It exhibited excellent selectivity and sensitivity to the NH$_3$ produced from tooth decay. Not to mention that BC/MXene aerogels were fully degradable in H$_2$O$_2$ solution and were environmentally friendly. Therefore, such MXene-based biosensors could serve as a helpful platform for the initial screening of dental diseases (Figure 18A,B).\[184\]

In fact, the functional groups present on the MXene surface were combined with bacterial cellulose via hydrogen bonding, then a composite aerogel was obtained by freeze-drying. The freezing methodology help to arrange cellulose along the ice grain boundary, leading to a porous 3D structure while embedding the MXene nanosheets into the cellulose layers. This type of preparation method improved the mechanical strength of the sensing platform as well (Figure 18C).\[184\]

Pressure-sensitive responses of the biosensor were investigated using finger bending, sound, and pulse as a trigger (Figure 18D–F). As shown, an enhanced response was achieved when the finger bending angle increased regularly, thus confirming their potential for motion monitoring (Figure 3D). A similar trend was obtained when the BC/MXene-based flexible sensor was affixed to the throat, vibration of the vocal cords during the speech was clearly and repeatedly detected by the sensor (Figure 3E). Moreover, real-time detection of the pulse signal was monitored when the sensor pasted to a wrist of a person (Figure 3F). Collectively, the MXene-integrated flexible biosensor had great potential for real-time detection of human health characteristics. In order to improve clinical diagnostic selectivity/sensitivity, antigen–antibody interactions are combined with electrochemical-based bioanalysis. These biosensors need low sample/reagent volume while possessing portability and cost-effectiveness.\[185\]

For instance, sulfur-doped MXene nanocomposite was fabricated as a platform of a typical immune-sensor, whereas procalcitonin antibody and its bioconjugates were applied for signal reinforcement. The dual effect of the MXene-based composite endowed the composites with increased surface conductivity and created more connection sites in the sensor.\[186\] In another work, palladium nanoparticles (Pd NPs) could be in situ generated by a Ti-based MXene nanosheet as an electrocatalyst to produce Pd@Ti$_x$C$_2$T$_y$ composite. The Pd NPs conferred MXene sheets high stability and increased catalytic activity for L-cysteine amino acid detection via facilitating fast-charge electron transfer. Collectively, the MXene acted as a reducing agent in situ generated by a Ti-based MXene nanosheet as an electrocatalyst to produce Pd@Ti$_x$C$_2$T$_y$ composite.

7. Concluding Remarks and Future Perspective

MXenes are an exciting class of 2D nanomaterials gaining interest in biomedical engineering applications, including regenerative medicine, infection treatment, cancer therapy, and biosensors. In addition, MXenes can be combined with other materials, which significantly boost their performances beyond individual counterparts in biomedical applications. For example, MXene-reinforced hydrogels represent a steppingstone to introducing breakthroughs in tissue engineering applications, bionics, and wearable medicine. This variety of applicability stems primarily from the unusual physical, chemical, mechanical, and electrical characteristics of MXene-reinforced hydrogels, which are critical for guiding cells into electroactive and load-bearing tissues or flexible bioelectronics.

The current developments of the MXene-reinforced composites are highly encouraging due to the promising outcomes in the treatment and diagnosis of different diseases. However, to proceed toward their clinical translation further, there are still
different challenges that should be addressed. For example, one of the main challenges of using these composites for cancer therapy and tissue regeneration is the lack of standard settings to be followed by all researchers for safety testing. Different studies have used different cell lines, different doses, or various animal models for the safety studies. In addition, toxicity assays are needed to be performed on both healthy and disease models. Moreover, since different composites are prepared using different MXenes under exposure to various chemicals and with different sizes and compositions, comprehensive studies are needed to establish correlations between the properties of composites, the experimental parameters, and their toxicity.

Formation of the MXene-reinforced composites may also end up in the non-biodegradable formulations, which are desirable for therapeutic and regenerative purposes. Unfortunately, the evaluation of biodegradation has been omitted from many studies on MXene composites. In addition, biosafety concerns at the cellular level are ignored in many cases. For example, how the surface charge, size, and thickness of the MXenes can affect their interaction with cells and different intracellular organelles, such as mitochondria and DNA, particularly in the long-term run. To become identified as “practically nontoxic,” these composites must also undergo a series of systematic biosafety studies on small and large animal models to understand their acute and chronic effects on different organs and various bio-systems, such as the nervous system and immune system. Additionally, while the final effect of MXene composites on cancer therapy, tissue repair, and infection therapy is well studied, the molecular mechanisms underlying these responses are poorly understood. They require close collaboration with molecular biologists to understand the precise treatment mechanisms fully. However, the fabrication of the MXene composites is still at its early stage, and the fabrication of ultrasmall MXene-based...
quantum dots and their usage in therapy and regeneration needs further attention. In addition, ultrasmall MXenes can be applied in diagnostic medicine, mainly through their surface modification or coating with different materials or targeting tools for prolonged circulation and accumulation in the site of interest for imaging purposes, allowing the design of novel theranostics. More research on MXene nanocomposites that can respond to NIR-II (1000–1700 nm) light is needed since they can be used for deep-tissue cancer and infection treatment at temperatures over 48 °C as well as tissue regeneration by local temperature modification at 38–40 °C. These particles can also be prepared in the future through hybridization with other elements, such as Ag, Bi, Au, etc., during the synthesis step to render various properties. Biosensing properties of the MXenes can also be tuned by changing their optical and electrical properties through the surface doping of various elements. The electrical and catalytic activities of MXenes have also recently attracted attention as sensitizers for photothermal cancer ablation, diagnostic multimaging, antimicrobial formulations, biosensing, and even as regenerative materials. Nevertheless, facile large-scale production with low price and new approaches for ease of surface engineering should be developed to move toward clinical translation and flourish as essential materials in biomedicine. We believe with the recent trust of the scientific community in the potential of MXenes, the above-mentioned challenges will be tackled soon, and the ongoing research progress in the field of MXene composites will lead to exceptional biomedical advances.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

2D materials, biological properties, biomedical applications, integrated composites, MXenes

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