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CLINICAL APPLICATIONS OF BIOMATERIALS

Review Article

MXenes in the application of diabetic foot: mechanisms, therapeutic implications and future perspectives

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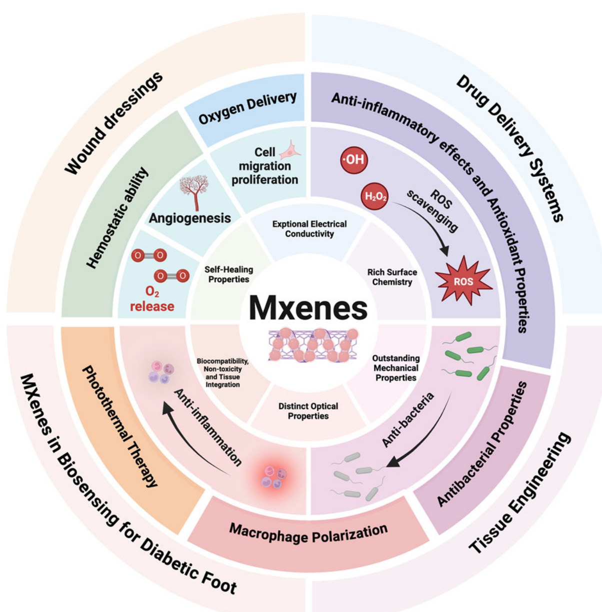
Abstract

Diabetic foot represents a significant healthcare challenge, accounting for a substantial portion of diabetes-related hospitalizations and amputations globally. The complexity of diabetic foot management stems from the interplay of poor glycemic control, neuropathy, and peripheral vascular disease, which hinder wound healing processes. The high incidence, recurrence, and amputation rates associated with diabetic foot underscore the urgency for innovative treatment strategies. Recent advancements in nanotechnology, particularly the emergence of MXenes (two-dimensional transition metal carbides and/or nitrides), have shown promising potential in addressing these challenges by offering unique physicochemical and biological properties suitable for various biomedical applications. It is a novel potential strategy for diabetic foot wound healing in the future. This review comprehensively summarizes current knowledge, unique characteristics, and underlying mechanisms of MXenes in the context of diabetic foot management. Additionally, we propose the potential application of MXenes-based therapeutic strategies in diabetes foot. Furthermore, we also provide an overview of their current challenges and the future perspectives in related fields of diabetic wound healing.

Graphical Abstract



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1 Introduction

Diabetic foot is a devastating complication of diabetes mellitus, affecting millions worldwide [1]. Diabetic wound management remains an extremely challenging clinical dilemma due to the complex interplay of impaired healing mechanisms, comorbidities, and the long-term consequences of diabetes [2, 3]. The normal wound healing process is a complex, orchestrated series of events that begins immediately after an injury, involving hemostasis, inflammation, proliferation, and remodeling phases [4, 5]. Initially, the body responds with hemostasis and inflammation, attracting immune cells to cleanse the wound and initiate blood clotting. This is followed by the proliferation phase, where new blood vessels form, collagen is deposited by fibroblasts, and epithelial cells migrate to cover the wound surface. Finally, in the remodeling phase, the collagen matrix is reorganized, scar tissue matures, and the wound site becomes stronger and more resilient, although not typically identical to the original tissue [6]. Thus, the management of diabetic foot requires multifaceted approaches, including wound dressing, infection control, and promotion of angiogenesis and tissue regeneration.

Wound dressing is a most critical therapeutic method to facilitate healing process. It can prevent wound infection from external contaminants and provide a moist environment for cell growth and tissue regeneration. Traditional dressings such as gauze and bandages can only protect the wound by absorbing exudate and shielding from external stimuli. In contrast, they exhibit limited oxygen permeability, inadequate adhesion and absence of biological activity [7, 8]. Therefore, innovative new wound dressings are urgently needed to overcome the limitations of conventional dressings. Recent advancements in nanotechnology, particularly the emergence of MXenes (two-dimensional transition metal carbides and/or nitrides), have shown promising potential in addressing these challenges by offering unique physicochemical and biological properties suitable for various biomedical applications. Different from other nanomaterials (such as graphene, metal nanoparticles, and polymeric nanoparticles), MXenes possess a comprehensive set of characteristics. For example, graphene has high electrical conductivity but may lack the biocompatibility and surface chemistry suitable for wound healing applications.

MXenes, a novel class of two-dimensional (2D) materials, have recently garnered significant attention for their unique physicochemical properties and potential applications in various fields [9]. They possess high surface area, excellent conductivity, tunable surface chemistry, and biocompatibility, making them attractive candidates for innovative therapeutic strategies in diabetic foot care. Currently, MXenes have been widely used in various fields such as biomedicine, water treatment, and food safety [10]. The continued exploration of MXenes' potential in these areas will pave the way for innovative solutions in the field of biomedicine. Particularly, more researchers have begun to investigate MXenes used in wounds healing because of their multifunctionality and easy surface functionalization capabilities [11].

This review comprehensively summarizes current knowledge, unique characteristics, and underlying mechanisms of MXenes in the context of diabetic foot management. And we also provide an overview of their current challenges and the future perspectives in related fields of diabetic wound healing.

2 Biological characteristics and functions of MXenes

2.1 Properties of MXenes

MXenes, a class of two-dimensional transition metal carbides, nitrides, and carbonitrides with the general formula Mn+1XnTx (where M represents a transition metal, X is carbon or/and nitrogen, and Tx denotes surface terminal groups such as -OH, -F, -O, etc.), have garnered significant attention since their discovery in 2011 due to their unique physicochemical properties (Fig. 1) [12, 13]. These materials exhibit exceptional properties, including high conductivity, large surface area, and unique surface chemistry, making them attractive for various applications [14].

Currently, two widely used methods for MXene synthesis are top-down synthesis and bottom-up synthesis. A reasonable synthesis method can better ensure the physicochemical properties of the synthesized material. The top-down synthesis method includes the etching of the MAX phase and the delamination of MXene, while bottom-up synthesis obtains 2D structures through a crystal growth process from small organic/ inorganic molecular/atomic structures [15]. Furthermore, surface modification can efficiently enhance various activities for specific biomedical applications [16].

2.2 Advantages of MXenes

MXene possesses various properties which make them suitable for wound healing. The following is a detailed exposition of the distinctive characteristics of MXenes (Fig. 2).

2.2.1 Exceptional electrical conductivity

MXenes exhibit metallic-like conductivity, with electrical conductivity reaching up to ~20,000 S/cm, surpassing even some forms of graphene. This high conductivity makes

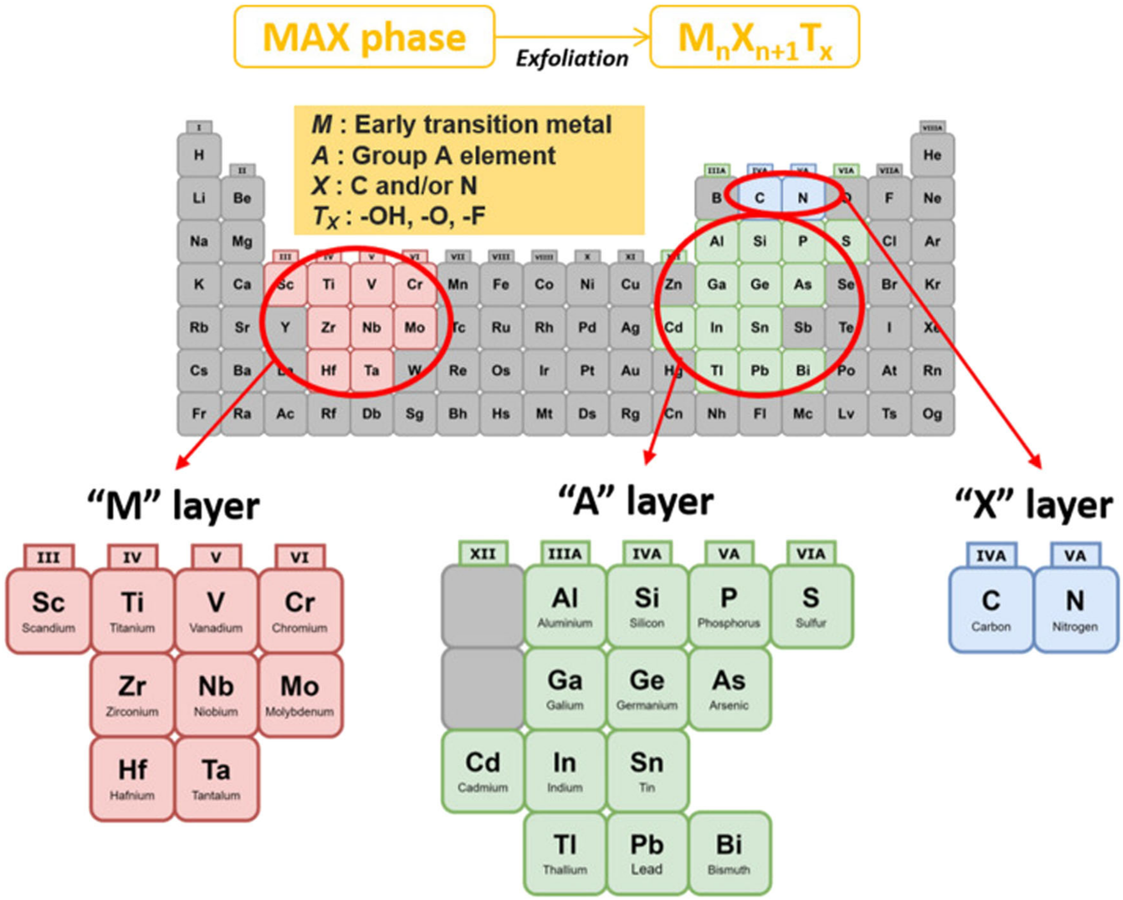


Fig. 1 General element composition of MAX phase and Mxene. Reproduced with permission [163]. Copyright 2021 BioMed Central

MXenes promising candidates for applications in electrochemical energy storage and electronic devices [17]. Inspired by mussel chemistry, Tang P et al. fabricated a polydopamine (PDA)-reduced graphene oxide (pGO)-incorporated chitosan (CS) and silk fibroin (SF) (pGO-CS/SF) scaffold. This scaffold was regarded as an efficient wound dressing due to their well physiological electrical signal transmission and antioxidant capacity [18]. Damage to the epithelium can generate endogenous direct current fields (DCEF) and transepithelial potential (TEP) difference to promote epithelial self-repair. Wound healing rate will decrease 25% when the electric field disappears. These epithelial cells manifest with directional migration after detecting electric field. Synchronously, electric field can accelerate wound healing by changing local microenvironment and promoting collagen synthesis [19]. The injurious endogenous electric field can promote the migration and proliferation of epithelial cells to achieve the wound healing [20]. The conductivity of MXenes is closely related to factors such as surface functional groups, size, and interlayer contact resistance. By controlling these factors, the conductive properties of MXenes can be further tuned. Single Ti3C2 layer has a low resistivity and a similar structure with semimetal. For Ti3C2Tx, proper band gap can be achieved by modifying the surface termination to change the conductivity [21]. When a wound occurs, the epithelial potential is immediately destroyed. and a new formed current circuit can be found at the edge of the wound [22].

Endogenous electric fields (EFs) can actively regulate the biological behavior of epidermal cells for wound healing. Thus, a series of electroactive and antibacterial dressings were designed for skin wound healing by using coaxial electrospinning. They can mimic skin functions and respond to the electrophysiological signals. Of them, Ti3C2Tx MXene/poly(e-caprolactone) (PCL)/gelatin-6 exhibited excellent conductivity and antibacterial activity to accelerate wound closure through physiological electrical signals [23]. When electrical stimulation was applied, 2D MXene films could significantly enhance the proliferation of neural stem cells (NSCs) and promote the neural differentiation [24]. Zheng et al. designed an injectable multifunctional hydrogel based on MXene@CeO2. This composite hydrogel had good electrical conductivity, antioxidant capacity, antibacterial properties and mechanical properties. In vivo experiment confirmed their promoting effect on wound

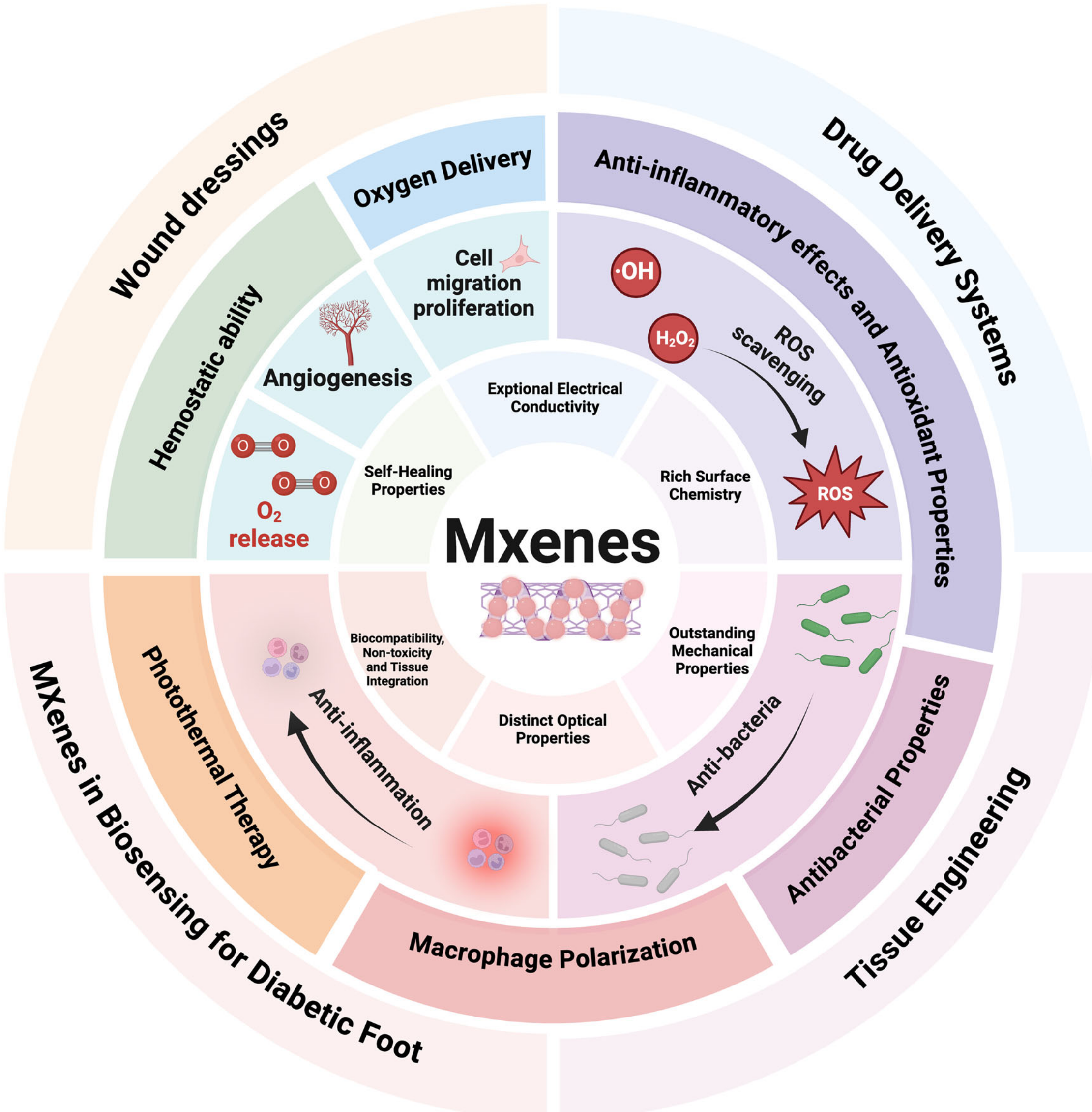


Fig. 2 Advantages of Mxenes

healing through promoting the proliferation and migration of fibroblasts [25]. Similarly, Liu et al. developed a multifunctional hydrogel, consist of polyvinyl alcohol (PVA) hydrogels with Ti3C2Tx (MXene) and polyaniline (PANI). PANI could enhance the mechanical properties through binding with PVA, while MXene provided conductivity and antibacterial activity. The stimulation of an applied electric field could promote cell proliferation and migration in vitro. And these effects collectively accelerated skin wound healing by promoting angiogenesis and collagen deposition [26]. And Zhu et al. developed a composite conductive hydrogel via incorporating two-dimensional (2D) MXenes into oxidized alginate and gelatin hydrogel. This composite conductive hydrogel exhibited good self-healing properties and promoting effect on mouse fibroblast (NH3T3s) to accelerate wound healing [27].

2.2.2 Rich surface chemistry

The ultrathin structure of MXenes endows them with an exceptionally high surface-to-volume ratio, enabling efficient interaction with biological molecules and cells [28]. The surfaces of MXenes are adorned with a variety of functional groups, including -OH, -F, -O, etc., which endow them with hydrophilic properties and chemical stability [29]. MXenes also have good hydrophilicity due to their surface functional groups and electronegative layered structures. They can disperse in water with cytocompatibility and adhesion [30]. The hydrophilic surface, which enables them to interact well with aqueous environments, such as wound exudates, facilitates their integration into wound dressings and promoting moist wound healing. Furthermore, the surface of MXenes also has a large number of binding sites to achieve material modification and drug delivery in the field of biomedicine [31].

By modulating the surface functional groups of MXenes, their physicochemical properties, such as conductivity and catalytic performance, can be significantly altered. Organic or inorganic materials can also be hybridized with MXenes to provide multifunctional and enhanced biocidal performances of wound dressings [32]. This tunability of surface chemistry offers possibilities for MXenes in multiple applications. Their surface modifications further enhance biocompatibility, allowing for controlled release of drugs and growth factors, accelerating healing processes.

2.2.3 Outstanding mechanical properties

MXenes inherit these excellent mechanical properties from their parent MAX phases, which are highly resilient layered conductive ceramics [33]. MXenes exhibit exceptional mechanical properties, including high strength and toughness. These properties make them potential candidates for use in composites and flexible electronic devices [34].

2.2.4 Distinct optical properties

MXenes possess extinction peaks in the ultraviolet-visible-near-infrared region, and their optical properties can be modulated through surface chemistry [35]. When exposed to light, MXenes absorb the energy of photons and interact with their lattice, causing an increase in particle temperature. The high specific surface area and abundant radical distribution of MXenes facilitate photothermal conversion, making them effective photothermal materials. These unique optical properties make MXenes potential candidates for applications in optoelectronics and photocatalysis. Ti3C2 nanosheets are regarded as a promising photothermal material due to their 100% photothermal conversion efficiency and 84% photo-water evaporation efficiency under solar irradiation [36]. Similarly, Nb2C nanosheets exhibit high photothermal stability with a photothermal conversion efficiency of 36.4% at NIR-I and 45.65% at NIR-II [37].

2.2.5 Biocompatibility, non-toxicity, and tissue integration

MXenes have shown good biocompatibility in preliminary studies, allowing for their integration with biological tissues without causing significant adverse reactions [38]. Recent studies have demonstrated the good biocompatibility and low cytotoxicity of MXenes, suggesting their potential for safe use in biomedical applications. Biocompatibility is a most critical parameter for widely biomedical applications. Li et al. designed an interfacial Schottky junction of Bi_2S_3/$Ti_3C_2T_x$ to effectively eradicate bacterial infection and accelerate wound healing. This composite material exhibited excellent cytocompatibility and biosafety in vivo or in vitro experiments [39]. When the mice were injected with Nb2CTx nanosheets, no significant changes have occurred in the hematological parameters and biochemical index. Exposure to Nb2CTx didn't result into significant inflammation [40]. Similarly, Zhang DK et al. treated human umbilical vein endothelial cells (HUVECs) with two different concentrations of Ti3C2Tx nanosheets (100 and 500 mg/L) and found none obvious acute cytotoxicity [41].

Of various two-dimensional transition metal compounds, Ti3C2 is still the main wound healing material in the MXene family, which is more toxic to cancer cell lines than normal cell lines. MXene (Ti3C2) manifested significant toxic effect to cancerous (A549 and A375) cell lines cell lines, and the toxic effect was dose-dependent [42]. Similarly, Szuplewska et al. also confirmed the similar conclusion [43].

Currently, most studies confirmed the non-cytotoxicity of MXenes composites. However, these conclusions are only based on cell experiments or short-term hematological assays. Long-term biosecurity and systematic evaluation are still needed.

2.2.6 Self-healing properties of MXenes

MXenes possess a unique self-healing ability due to their layered structure and strong interlayer interactions [44]. When a crack or damage occurs, the layers can slide and realign, restoring the material's integrity and functionality. The self-healing properties of MXenes make them attractive for use in biomedical devices, where durability and long-term performance are crucial. Devices coated or incorporating MXenes could self-repair in response to damage, extending their lifespan and reducing the need for frequent replacements [45]. Among these properties, tissue adhesion and self-healing capabilities have emerged as particularly promising features for biomedical applications.

Currently, MXenes have achieved wide range of applications in different fields due to its unique properties and versatility, including energy storage, biomedical, electromagnetic shielding, and flexible electronic devices. In addition, the magnetic properties of MXenes are usually ignored due to limited experimental data. But they exhibit various application potentials in cancer theranostics and nanoelectronic devices [46].

2.3 Underlying mechanisms of MXenes in diabetic foot wound healing

MXenes have emerged as promising candidates for diabetic foot wound healing due to their unique properties. They can trigger a series of changes in the local microenvironment for advanced wound care, including oxygen delivery, anti-inflammatory effects, antioxidant properties, antibacterial properties, macrophage polarization, photothermal therapy, and hemostatic ability.

2.4 Oxygen delivery

Long-term hypoxia will hinder diabetic wound healing through inhibiting angiogenesis and epithelialization. MXenes have been explored as oxygen carriers and photothermal agents in the field of diabetic foot wound healing. MXenes possess unique properties that make them suitable for this application. Their high surface area and ability to adsorb and release oxygen make them effective oxygen carriers. This is particularly important in diabetic foot wounds, where hypoxia (low oxygen levels) is a common issue that can impede the healing process. By delivering oxygen to the wound site, MXenes may help to create an environment that is more conducive to healing. Researchers have investigated their potential to facilitate and enhance the healing process by delivering oxygen to the wound site and harnessing their photothermal properties to promote tissue repair and regeneration. For instance, an injectable hydrogel based on hyaluronic acid-dopamine (HA-DA) and poly-dopamine (PDA)-coated Ti3C2 MXene nanosheets, catalyzed by an oxyhemoglobin/hydrogen peroxide (HbO_2/H2O2) system, demonstrates efficient oxygen delivery upon near-infrared (NIR) radiation. This system not only provides a controlled release of oxygen but also scavenges reactive oxygen species (ROS), mitigating oxidative stress and promoting wound healing (Fig. 3) [47]. X Wang et al. developed a MXene/Polydimethylsiloxane/Polydopamine/Polyurethane Sponge (MXene/PDMS/PDA/PU) nanocomposite, which has excellent flexibility and breathability. The breathability endowed this

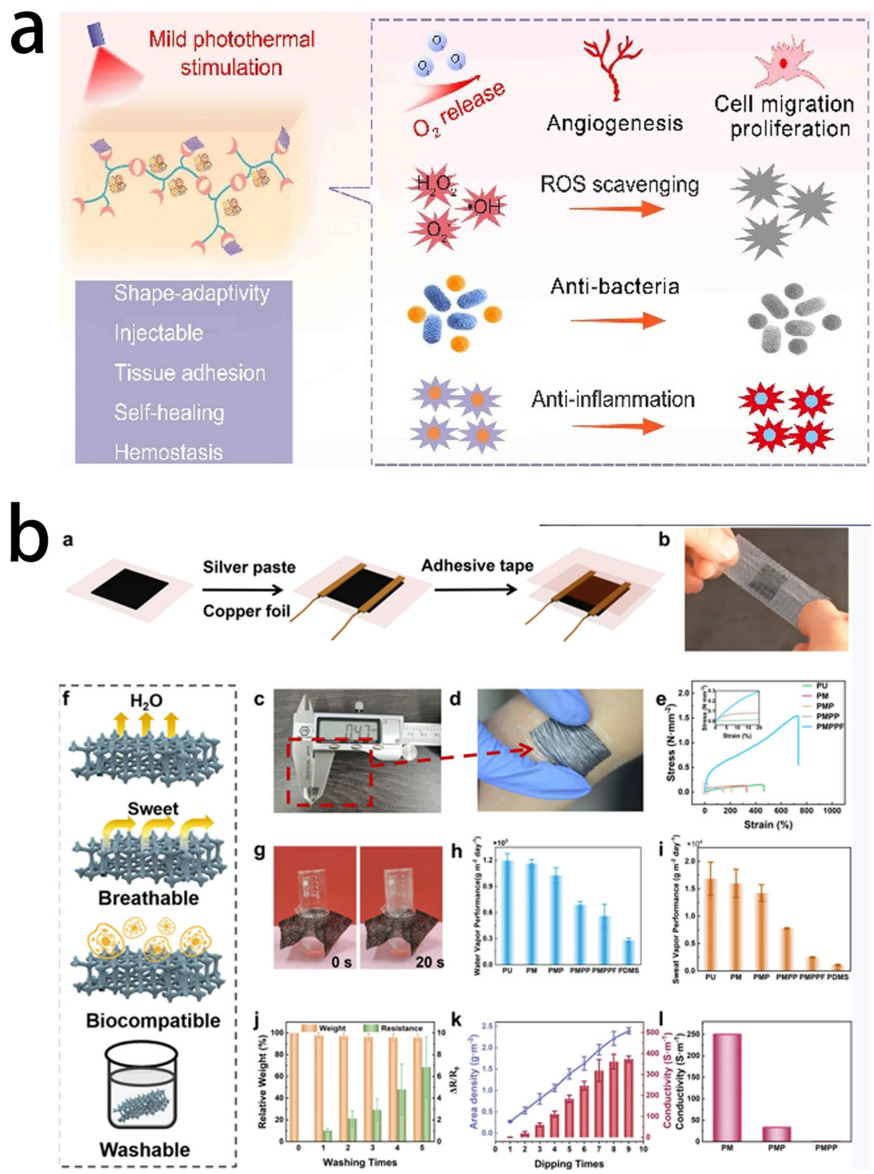


Fig. 3 Oxygen Delivery of MXenes in diabetic foot wound healing. **a** HA-DA coated Ti3C2 MXene nanosheets provide oxygen repeatedly under NIR. Reproduced with permission [47]. Copyright 2022 American Chemical Society. **b** MXene/PDMS/PDA/PU nanocomposite had excellent breathability and oxygen supply capacity. Reproduced with permission [48]. Copyright 2022 Springer Nature

nanocomposite with oxygen supply capacity for wound healing [48]. Furthermore, MXene could induce angiogenesis to accelerate wound healing through electrical stimulation, which supplies sufficient oxygen and nutrients. It has excellent electrical conductivity (Fig. 3) [49]. Liu et al. developed a polyvinyl alcohol/MXene(Ti3C2Tx)/polyaniline (PMP) hydrogel for skin wound healing. Of them, PANI acted as an electrical conductor to stimulate angiogenesis for wound [26].

In conclusion, MXenes as oxygen carriers offer a novel approach to facilitating diabetic foot wound healing. Their unique properties make them a promising candidate for addressing the challenges associated with these wounds. As research in this field continues to advance, the potential of MXenes in improving the outcomes of diabetic foot wound healing becomes increasingly evident.

2.5 Anti-inflammatory effects and antioxidant properties

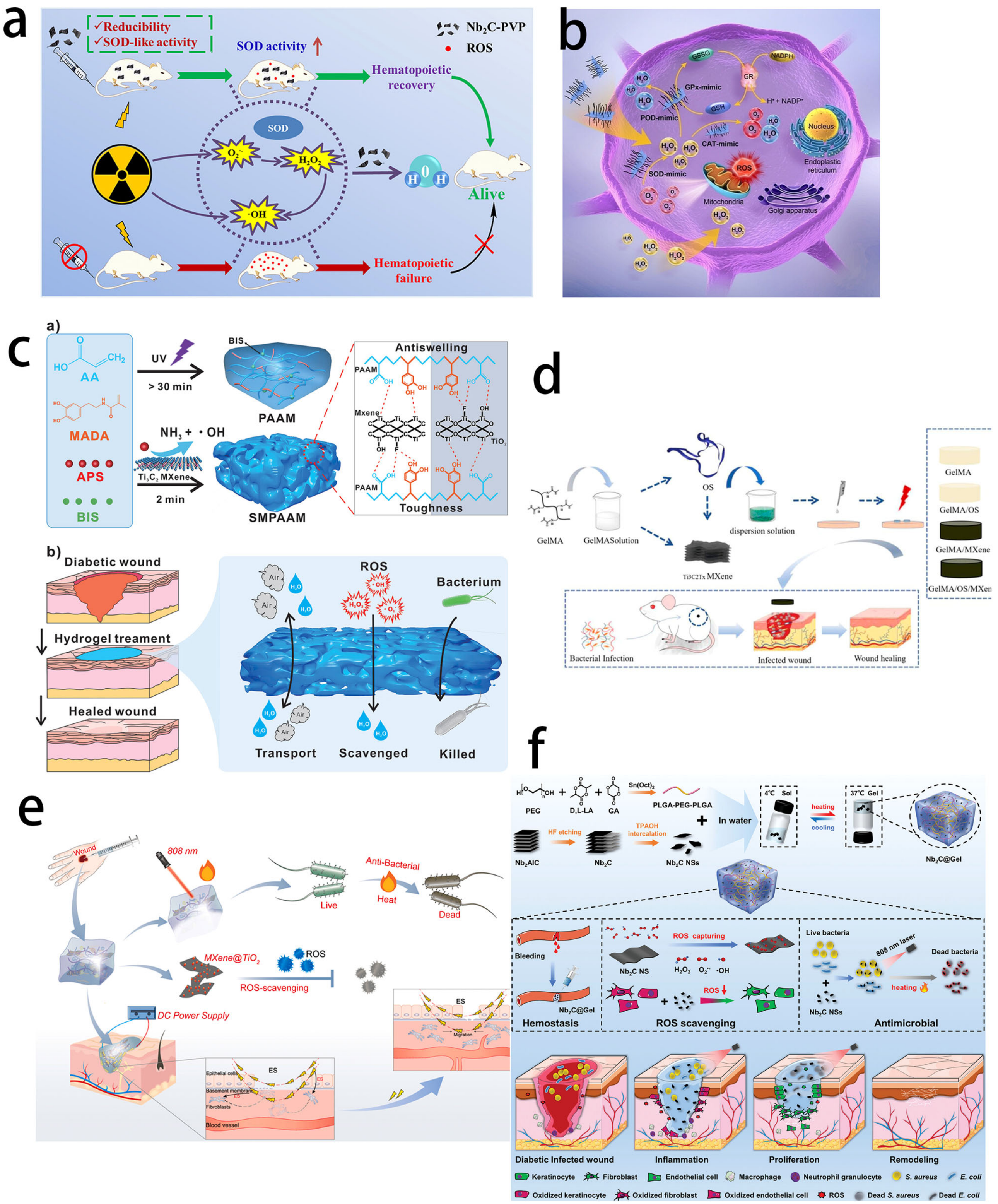
In the healing process of wound, inflammatory response exhibits a dynamic balance with different pathophysiological effects in various stages. The local inflammatory response can conduct the migration of inflammatory cells to remove wound cell debris and foreign substances at the earlier stage [50]. In the contrast, inflammatory cells will be gradually replaced by transplanted fibroblasts and epithelial cells to achieve re-epithelialization and wound healing at latter stage.

When the dynamic balance was destroyed, excessive production of reactive oxygen species (ROS), pro-inflammatory cytokines, and protease will hinder wound healing due to causing oxidative damage of cells and tissues [51, 52]. The excessive oxidative stress will hinder the process of wound healing by limiting angiogenesis and causing irreversible oxidative damage to cells [53].

Reactive oxygen scavenging ability is usually employed to accelerate wound healing. MXenes exhibit better reactive oxygen scavenging due to their rich functional groups on the surface [54]. MXenes can modulate the micro-environment by regulating the release of inflammatory mediators (cytokines and chemokines) and immune response [55]. The ultrathin two-dimensional (2D) niobium carbide (Nb_2C) MXene can scavenge free radicals (such as hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$), and superoxide radicals ($O_2^{\bullet-}$).) against ionizing radiation (IR) (Fig. 4) [56]. Similarly, Yang et al. also confirmed that Nb2C MXenzyme could eliminate reactive oxygen species and inhibit inflammatory factors. It exhibited superoxide dismutase-, catalase-, glutathione peroxidase-, and peroxidase-activities (Fig. 4) [57].

Adding MXene to skin wound dressing is a promising strategy to accelerate wound healing by improve the overall scavenging ability of ROS. Li et al. engineered a unique biological metabolism-inspired hydrogel to ameliorate hostile local microenvironment of reactive oxygen species (ROS) accumulation and chronic hypoxia [58]. Wei et al. added Ti_3C_2MXene into a novel sponge-like macro-porous hydrogel (SM-hydrogel). This composite hydrogel had a reactive oxygen scavenging rate up to 96% at 2 h due the electron transport capability of MXene. The antioxidant phenol quinone groups on the surface are the main reason for removing ROS, while MXenes could further enhance the removal ability (Fig. 4) [59]. Liang et al. incorporated tick-derived antibacterial polypeptides (Os) and MXene nanoparticles to GelMA hydrogel. It simultaneously possessed excellent antibacterial and tissue regenerative activities (Fig. 4) [60].

Several novel multifunctional hydrogels are also designed to enhance wound healing. GA/OKGM/MT hydrogel was fabricated composed of MXene@TiO2 (MT), gelatin (GA), and oxidized konjac glucomannan (OKGM). This composited hydrogel exhibited multi-functions, including fast hemostasis, anti-inflammatory effect, and antibacterial activity. The MT endowed the composite hydrogel with good photothermal ability to help wound healing process (Fig. 4) [61]. Li et al. fabricated an injectable hydrogel based on hyaluronic acid-*graft*-dopamine (HA-DA) and polydopamine (PDA) coated Ti_3C_2 MXene nanosheets. This composite material could sustainably release oxygen and scavenge excessive reactive nitrogen species and ROS (such as H_2O_2, $O_2^{\bullet-}$, and $^{\bullet}OH$) to ensure the healing of diabetic infected wounds. Scavenging ROS was able to achieve and maintain the intracellular redox homeostasis. In addition, it could also regulate macrophage polarization from M1 to M2 to achieve anti-inflammation [47]. Chen et al. developed a temperature-sensitive Nb2C hydrogel, consisting of Nb2C and poly (lactic-co-glycolic acid) (PLGA)-polythene glycol (PEG)- PLGA triblock copolymer. The antioxidant activities of Nb2C nanosheets synergistically promoted diabetic wound healing through eliminating reactive oxygen species (ROS) and reducing oxidative damage. It also exhibited excellent antibacterial activity against both Gram-positive and Gram-negative bacteria to accelerate wound healing (Fig. 4) [62]. X Yang et al. fabricated a multiple stimuli-responsive MXene-based hydrogel for deep chronic wound healing. As an intelligent drug delivery carrier, it had excellent photo- and magnetic-responsive abilities to promote the wound healing. In vivo or in vitro experiments had also confirmed the effective wound healing ability [63]. Liu et al. developed a Cu(II)@MXene photothermal complex as antibacterial dressing. It could accelerate infected wound healing through photothermal antibacterial, ROS scavenging, and angiogenesis-promoting activities. In vivo experiments also confirmed their multifunction [64].



MXenes possess large specific surface areas and abundant surface terminal groups. They can react with free radicals through their surface terminal groups (such as -OH, -O, -F, etc.), thereby scavenging reactive oxygen species (ROS) and free radicals in the body and reducing oxidative stress-induced cellular damage. The self-structure and functional groups on the surface can regulate the ROS scavenging ability of MXene-based materials. Studies have

◀ **Fig. 4** Anti-inflammatory effects and antioxidant Properties of MXenes in diabetic foot wound healing. **a** Nb_2C-PVP NSs scavenged free radicals (such as H_2O_2, $^{\bullet}OH$, and $O_2^{\bullet}$) with intrinsic radio-protective nature in vivo. Reproduced with permission [56]. Copyright 2019 American Chemical Society. **b** Nb2C MXenzyme eliminated ROS and inhibited inflammatory factors, exhibiting superoxide dismutase-, catalase-, glutathione peroxidase-, and peroxidase-activities. Reproduced with permission [57]. Copyright 2023 John Wiley and Sons Ltd. **c** The MXene-induced SM-hydrogels had a reactive oxygen scavenging rate up to 96% at 2 h. Reproduced with permission [59]. Copyright 2022 John Wiley and Sons Ltd. **d** Liang et al. incorporated tick-derived antibacterial polypeptides (Os) and MXene nanoparticles to GelMA hydrogel. It simultaneously possessed excellent antibacterial and tissue regenerative activities. Reproduced with permission [60]. Copyright 2022 Frontiers Media S.A. **e** GA/OKGM/MT hydrogel exhibited multi-functions, including fast hemostasis, anti-inflammatory effect, and antibacterial activity. Reproduced with permission [61]. Copyright 2024 Elsevier Ltd. **f** The temperature-sensitive Nb2 C@Gel promoted diabetic wound healing through eliminating ROS and excellent antibacterial activity [62]. Copyright 2022 Wiley-VCH GmbH

shown that Ti3C2 MXene nanosheets significantly reduce intracellular ROS levels, protecting cells from oxidative stress-induced damage [65]. However, surface chemistry enhances the anti-inflammatory effects and targeted ability. New functional groups on the surface also increase the biocompatibility by avoid potential ROS damage from self-release [66]. Thus, surface modification may be a critical approach to achieve enhanced biocompatibility and antioxidant applications.

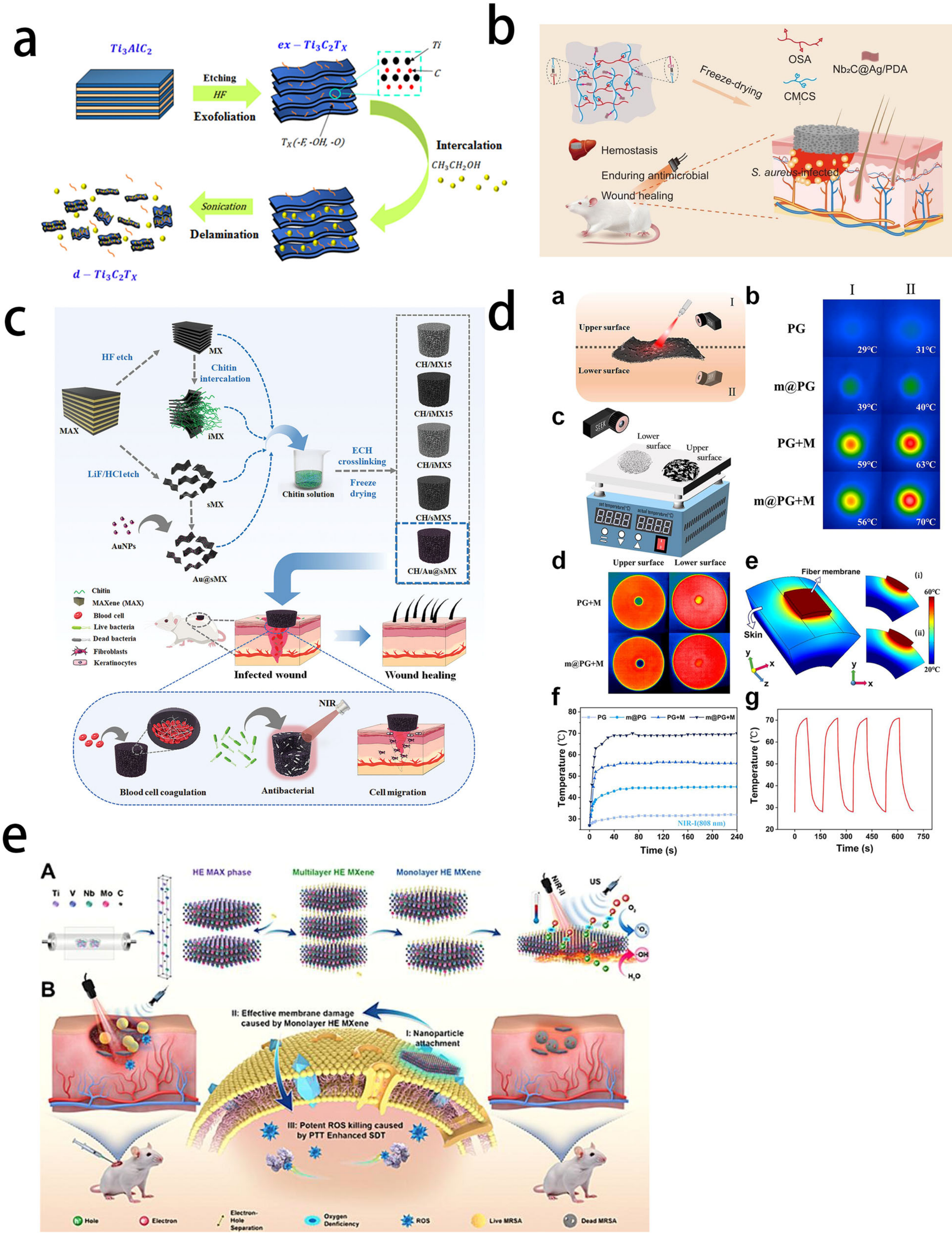
In conclusion, MXenes can facilitate healing by modulating inflammation, scavenging reactive oxygen species, and potentially enhancing cell proliferation and migration. Additionally, MXenes' sharp edges physically disrupt bacterial membranes as "nanoknife effect" while their ROS-generating ability chemically kills pathogens. Future research directions encompass elucidating their detailed molecular mechanisms and designing targeted delivery systems for enhanced therapeutic outcomes in wound management.

2.6 Antibacterial properties

To date, infection remains a main factor that hinders wound healing. And antibiotics are widely used to prevent and treat wound infections and protect granulation tissue formation. However, the misuse and abuse of antibiotics usually lead to dire consequences, including the emergence of bacterial resistance and biofilm infection [67]. The significance and challenges of bacterial infection treatment in diabetic foot ulcers lie in their intricate interplay with the underlying diabetic condition. As the conventional drugs unpredictably lost their places, an immediate contemporary approach is urgently needed to resolve this menace [68]. As an innovative therapeutic strategy, nanotechnology provides potential promise drugs.

MXenes also exhibit great potential in antibacterial applications due to their unique two-dimensional layered structure, large surface area, abundant surface terminal groups, and excellent photothermal and photoelectronic properties. Ti3C2Tx has higher antibacterial efficiency against gram-negative or positive bacteria, with antibacterial efficiency even higher than that of widely reported antibacterial agent graphene oxide. And the antibacterial activity is dose-dependent [69]. Cell damage or death could be found just after the Ti3C2Tx was added in bacterial cultures. The number of bacterial colonies decreased with increasing concentration of Ti3C2Tx. In addition, MXene also has antifungal properties. Lim GP et al. reported that delaminated Ti3C2Tx MXene nanosheets (d-Ti3C2Tx) had antifungal activity against Trichoderma reesei. And the spores of the fungi did not germinate after treated with d-Ti3C2Tx MXene nanosheets (Fig. 5) [70].

The antibacterial mechanisms of MXenes include: i) Physical Disruption: The sharp edges of MXene nanosheets can directly tear bacterial cell membranes, leading to the leakage of cytoplasmic contents and subsequent bacterial death [71]. As a "Nano-knife", the sharp edges of MXene can Mechanically disrupt the bacterial membrane, leading to cytoplasmic leakage and bacterial DNA release (Fig. 6) [69]. And the antimicrobial activity was size-dependent and exposure time-dependent. Shamsabadi et al. detected the antibacterial properties of MXene nanosheets with four different lateral sizes. They confirmed that direct physical interactions between the MXene nanosheets and bacteria cells were a main mechanism against E. coli and B. subtilis in dark conditions. Meanwhile, the antibacterial activity was related with both size- and exposure time. Bacteria cell dispersion was observed after bacterial DNA leakage from the cytosol occurred within 3 h [72]; ii) Chemical Inactivation: MXenes can generate reactive oxygen species (ROS), which disrupt bacterial cell structures, resulting in bacterial death. Excessive ROS leads to mitochondrial dysfunction, which can kill cell through inducing oxidative damage to biomacromolecules and cell membranes [73]. As a novel antibacterial concept, exogenous reactive oxygen species (ROS) can be used to kill bacteria. Yang et al. fabricated a quad-channel synergistic antibacterial nanoplatform of Ti_3C_2 MXene/MoS_2(MM) 2D bio-heterojunctions (2D bio-HJs). It had photothermal, photodynamic, peroxidase-like (POD-like), and glutathione oxidase-like properties. The local increased ROS and heating could synergistically inactive the bacteria under near-infrared (NIR) laser irradiation. The cytocompatibility and anti-bacterial were confirmed in vivo and vitro tests (Fig. 6) [74]; iii3) Photothermal Effect: MXenes possess excellent photothermal conversion capabilities and can generate heat under illumination, further enhancing their antibacterial activity. Photothermal properties of MXenes



can significantly inhibit bacterial activities through interfering with cell structures and substances [75]. MXenes can efficiently convert light energy into localized heat under NIR irradiation. It selectively targets and eliminates bacteria through damaging their membranes or denaturing essential proteins [76].

◀ **Fig. 5** Antibacterial mechanisms of MXenes in Diabetic Foot Wound Healing. **a** The d-Ti3C2Tx had antifungal activity against Trichoderma reesei and its spores. Reproduced with permission [70]. Copyright 2020 Elsevier Ltd. **b** OSA/CMCS-Nb2C@Ag/PDA composite aerogel exhibited approximately 100 % inhibition of Staphylococcus aureus and Escherichia coli under NIR irradiation. Reproduced with permission. Reproduced with permission [78]. Copyright 2024 Elsevier B.V. **c** Ag NPs/MXene was added into the network of chitin sponge to improve the antibacterial activity. Reproduced with permission [81]. Copyright 2022 Wiley-VCH GmbH. **d** The combination of Ti3C2Tx MXene and fibers is designed to reduce tumor recurrence rate and accelerate surgical wound healing. Reproduced with permission [83]. Copyright 2023 Elsevier. **e** TiVNbMoC3 MXenes could kill Methicillin-resistant Staphylococcus aureus (MRSA) and its biofilm via increasing ROS release in response to US and NIR-II irradiation. Reproduced with permission [85]. Copyright 2024 Elsevier BV

The antibacterial effects of PDA-coated MXenes further prevent wound infection, a common complication in diabetic foot ulcers [77]. Li et al. fabricated an OSA/CMCS-Nb2C@Ag/PDA (OC/NAP) composite aerogel consisting of sodium alginate oxide (OSA), carboxymethyl chitosan (CMCS), and Nb2C@Ag/PDA (NAP). OC/NAP composite aerogel exhibited approximately 100 % inhibition of Staphylococcus aureus and Escherichia coli under NIR irradiation (Fig. 5) [78]. Feng developed a MXene@AgNWs@PAAM@resveratrol hydrogel with superior wound healing properties. MXene acted as structural enhancers, while silver nanowires (AgNWs) exhibited antibacterial properties. This composite material showed exceptional wound-fitting capabilities and impressive mechanical stretchability [79].

In addition, other antibacterial agents or therapeutic strategies are doped into MXene-based flexible biomaterials to enhance MXene's own antibacterial properties. C Guo et al. developed a novel multimodal antibacterial platform, consisting of zinc-based metal-organic framework (Zn-MOF), curcumin, and Ti3C2Tx nanosheets (NSs) for bacteria-infected wound healing. This composite material released Zn2+ and curcumin in a controlled and accelerated manner through excellent photothermal performance under NIR irradiation [80]. Li et al. added gold nanoparticles (AuNPs)-modified MXene nanosheets (Ag NPs/MXene) into the network of chitin sponge, which significantly improved the antibacterial activity (Fig. 5) [81]. Xu et al. developed an antibacterial nanofibrous membrane (MXene-AMX-PVA nanofibrous membrane), consists of amoxicillin (AMX), MXene, and polyvinyl alcohol (PVA). The MXene converted near-infrared laser into heat, which could increase the release of AMX and destroy the noncellular components of bacteria. This composite nanofibrous membrane exhibited an excellent synergistic antibacterial effect to accelerate wound healing [82].

The hybridization of MXenes with other materials can provide synergistic effects and enhance antibacterial performance. For example, MXene-based nanocomposite hydrogels have been used in wound healing, showing excellent antibacterial properties and biocompatibility [15]. In addition, the residual cancer cells and possible wound infection are unavoidable after surgical excision of skin melanoma. The novel composite materials by combining Ti3C2Tx MXene and fibers (including PLA and gelatine) are designed to reduce tumor recurrence rate and accelerate wound recovery, which have asymmetric and unidirectional thermal conductivity. It could simultaneously regulate the heat both on the upper surface and the lower surface of the fiber membrane. This combined effect thus effectively clean up cancer cells, inhibits the post-surgical tumor recurrence, and accelerates surgical wound healing [83].

As a common noninvasive therapy, sonodynamic therapy (SDT) has a remarkable tissue penetration capability and potential antibacterial activity via producing ROS [84]. MXenes can also be considered as a new type of sonosensitizer. W Song et al. fabricated a TiVNbMoC3 MXenes (TVNMC) to achieve antibacterial activity through the generation of reactive oxide species (ROS). This composition releases ROS under US irradiation during the energy storage and conversion. The ROS release could also be enhanced in response to US and NIR-II irradiation. TVNMC MXene could kill Methicillin resistance Staphylococcus aureus (MRSA) and its biofilm to promote wound healing (Fig. 5) [85].

MXenes are best alternatives to antibiotics for eliminating drug-resistant bacteria. MXenes have potential applications in non-invasive strategies against antibiotic-resistant pathogens. Zhong et al. developed a new MXene-doped composite microneedle (MN) patch for drug-resistant bacteria infected wound healing. This multifunctional MN exhibited excellent mechanical strength and photothermal antibacterial and ROS removal properties for promoting wound healing [86]. MXenes can convert the adsorbed UV-visible light into heat and kill the bacteria through damaging bacterial membrane.

In summary, Researchers are continually refining MXene-based nanoplatforms, such as by integrating them with other nanomaterials like Pt nanoparticles, to enhance their therapeutic effects and broaden their response to different laser wavelengths, thereby achieving more effective bacterial clearance in deep tissues. Additionally, the development of MXene-based composites with enhanced antibacterial properties and biocompatibility could lead to innovative wound dressings and other medical devices that promote healing and prevent infections. Moreover, as research progresses, MXenes may also find applications in other anti-infectious strategies, such as chemodynamic therapy (CDT) or in combination with other therapeutic modalities for synergistic effects.

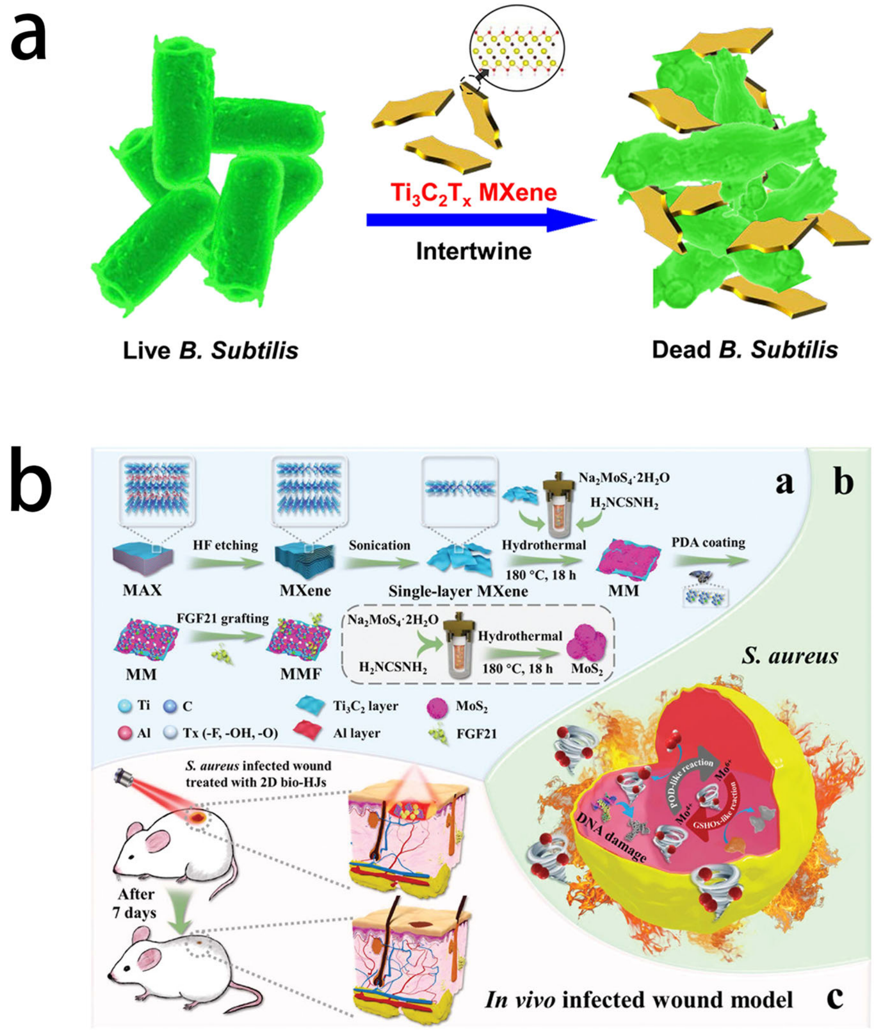


Fig. 6 Antibacterial mechanisms of MXenes. **a** As a "Nano-knife", the sharp edges of MXene can mechanically disrupt the bacterial membrane, leading to cytoplasmic leakage and bacterial DNA release. Reproduced with permission [69]. Copyright 2016 American Chemical Society. **b** Ti_3C_2 MXene/MoS_2(MM) 2D bio-heterojunctions synergistically inactivated the bacteria under NIR via increasing local ROS and heating. Reproduced with permission [74]. Copyright 2021 Wiley-VCH GmbH

2.7 Macrophage polarization

Macrophages, as key immune cells in the body, play a crucial role in maintaining tissue homeostasis and responding to various stimuli [87]. They can polarize into different phenotypes, typically classified as M1 (classically activated) and M2 (alternatively activated) macrophages, in response to different microenvironments and signals. M1 macrophages are associated with inflammation and host defense, secreting pro-inflammatory cytokines and mediating tissue damage [88]. Conversely, M2 macrophages are involved in tissue repair, wound healing, and immune regulation, secreting anti-inflammatory cytokines and promoting tissue remodeling [89]. The HA-DA component in the hydrogel system can regulate macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, leading to reduced inflammation and improved wound healing outcomes [90]. M2 macrophages can accelerate wound healing by recruiting endothelial cells and fibroblasts to the wound site. And this process significantly promotes the synthesis of extracellular matrix (ECM) and granulation tissue [91]. Natural polymers (hydrazide-modified hyaluronic acid and aldehyde modified hyaluronic acid) and a metal-organic frameworks-derived catalase-mimic nanozyme (ε-polylysine coated mesoporous manganese cobalt oxide) were embedded in hydrogels to prevent damage from ROS and hypoxia. This hydrogel also induced the macrophages polarization from pro-inflammatory phenotype (M1) to anti-inflammatory sub-type (M2) to promote proliferation, neovascularization, and re-epithelialization [58]. This immunomodulatory effect is crucial in the complex wound healing process of diabetic foot ulcers. And the balance of M1 and M2 macrophages is often disrupted and triggers an overproduction of pro-inflammatory cytokines. Reducing excessive inflammation is crucial to promote angiogenesis and reduce the risk of infection [92].

MXenes, with their unique physicochemical properties, have been investigated for their potential to influence macrophage polarization. The interaction between MXenes

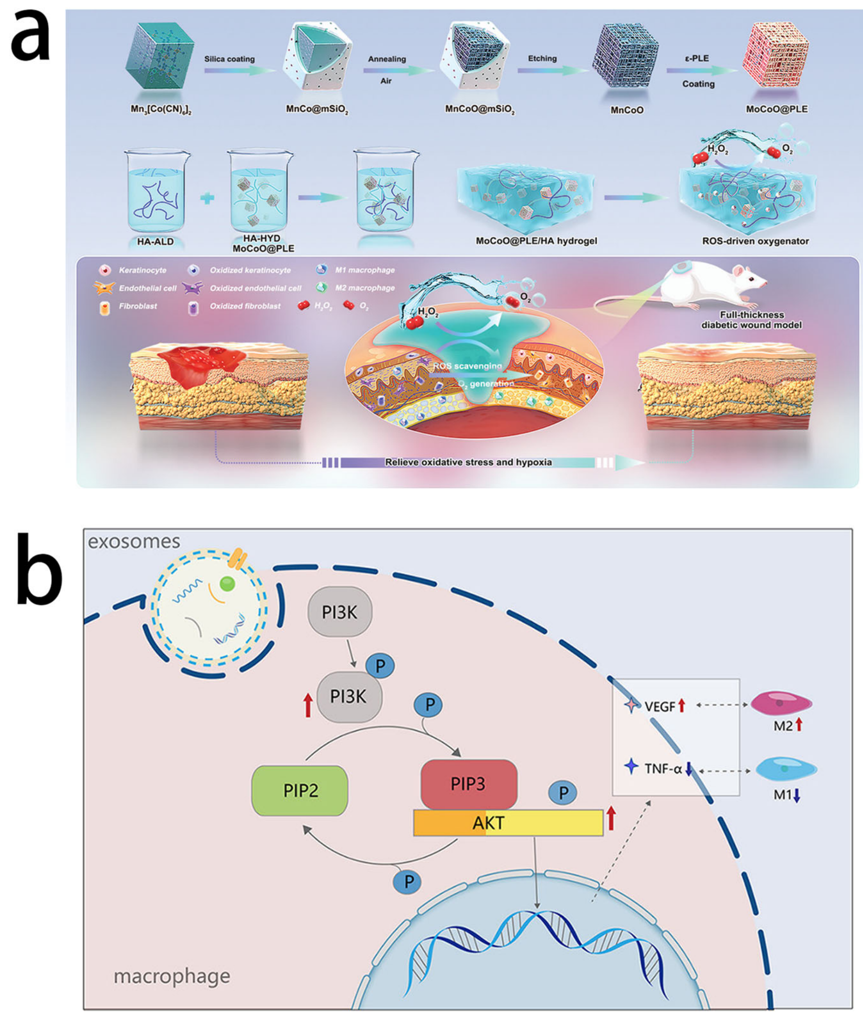


Fig. 7 Macrophage Polarization of MXenes in Diabetic Foot Wound Healing. **a** The engineered nanozyme-reinforced hydrogels prevent damage from ROS and hypoxia. This hydrogel also induced the macrophages polarization from M1 to M2. Reproduced with permission [58]. Copyright 2022 John Wiley and Sons Ltd. **b** This FM-Exo hydrogel exhibited injectable, thermosensitive, self-healing properties, and could sustainably release M2-Exo to elevate the proliferation and migration of fibroblasts and HUVECs. Reproduced with permission [96]. Copyright 2024 American Chemical Society

and macrophages may lead to phenotypic changes in macrophages, affecting their function and subsequent immune responses [93]. Certain MXenes, such as Ti3C2, have been reported to promote macrophage polarization towards an M2-like phenotype. This polarization is characterized by increased expression of M2-associated markers and secretion of anti-inflammatory cytokines. The mechanism underlying MXene-induced macrophage polarization may involve the activation of specific signaling pathways, such as the PI3K/Akt pathway, which is known to regulate macrophage polarization. By promoting M2 macrophage polarization, MXenes may contribute to a more favorable microenvironment for tissue regeneration and repair, enhancing the healing process [94]. Chin et al. also reported that MXenes can induce macrophages from the pro-inflammatory (M1) phenotype to the anti-inflammatory (M2) phenotype, which promotes wound healing through reducing excessive inflammation [95]. The potential of MXenes to influence macrophage polarization is exciting, particularly towards an M2-like phenotype. This property holds promise for various therapeutic applications, including tissue repair and immune modulation. Jiang X et al. fabricated a F127-MXene M2 macrophages exosomes (FM-Exo) hydrogel nanocomposite with an M2-Exo sustained-release property. This FM-Exo hydrogel exhibited injectable, thermosensitive, self-healing properties and could sustainably release M2-Exo to elevate the proliferation and migration of fibroblasts and HUVECs. These properties ultimately enhanced the diabetic wound healing through VEGF secretion and enhanced proper collagen deposition (Fig. 7) [96].

However, several challenges need to be addressed before their clinical translation. The long-term effects and biosafety of MXenes in biological systems need to be thoroughly evaluated to ensure their safe use in therapeutic applications. Preclinical studies in animal models are essential to validate the effects of MXenes on macrophage polarization and to assess their efficacy and safety in relevant disease models. Meanwhile, further research is needed to elucidate the exact mechanisms underlying MXene-induced macrophage polarization, including the specific signaling pathways involved and the role of MXene surface chemistry.

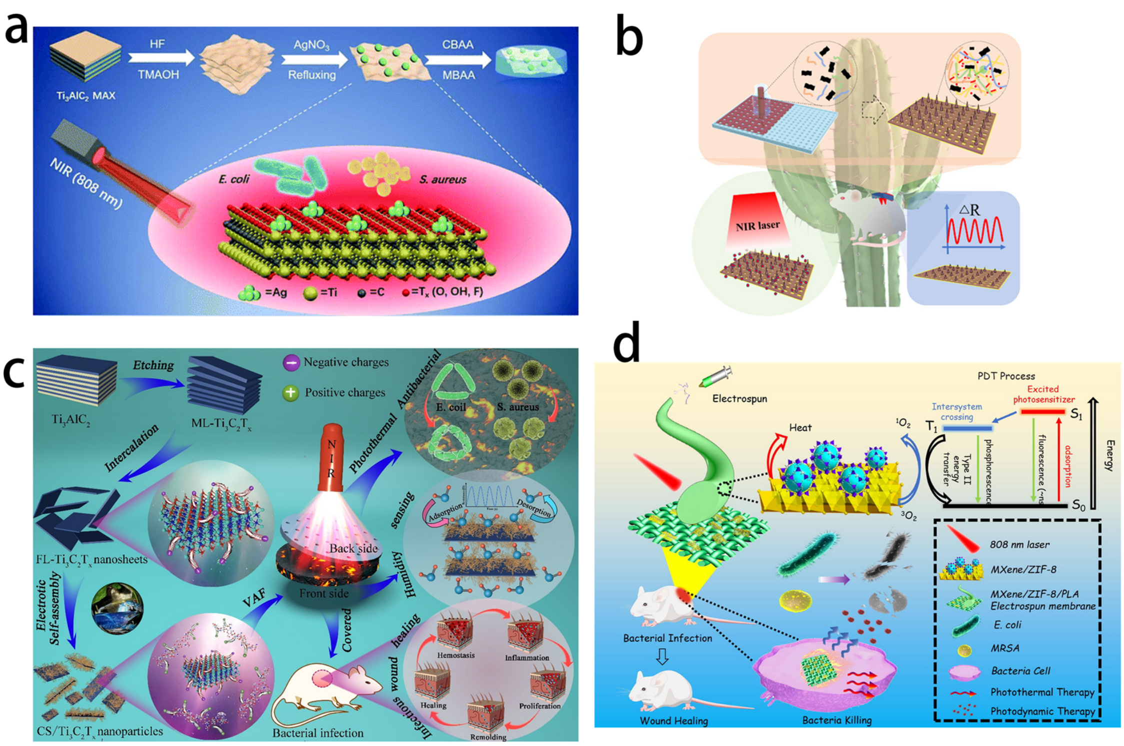


Fig. 8 Photothermal Therapy of MXenes in Diabetic Foot Wound Healing. **a** The antibacterial activity of Ti3C2Tx and Ag/Ti3C2T was enhanced under near-infrared light exposure. Reproduced with permission [100]. Copyright 2020 Royal Society of Chemistry. **b** MXene and spidroin-incorporated microneedle scaffolds exhibited photothermal responsive and self-healing properties for promoting wound healing. Reproduced with permission [102]. Copyright 2022 Royal Society of Chemistry. **c** P-CM membrane exhibited self-standing ability, good flexibility, biocompatibility, excellent photothermal antibacterial properties. Reproduced with permission [104]. Copyright 2022 Elsevier Ltd. **d** A MXene/ZIF-8/PLA composite membrane exhibited well photothermal (PTT) convention efficiency and bactericidal rate, respectively. [105]. Copyright 2021 Elsevier Inc

2.8 Photothermal therapy

MXenes exhibit an excellent photothermal effect to enhance wound healing. The photothermal effect also stimulates various cellular processes involved in tissue regeneration. It enhances the blood flow, induces collagen remodeling, and the synthesis of extracellular matrix components [97]. When exposed to light, they can absorb and convert it into heat, which can be used to stimulate tissue repair and regeneration [98]. This photothermal effect has been shown to promote cell proliferation and migration, as well as increase blood flow to the wound site, all of which are crucial for successful wound healing.

As an alternative antibacterial strategy, photothermal therapy (PTT) demonstrates significant potential in wound antibacterial treatment. It can leverage light-to-heat conversion agents to eradicate bacteria through localized heating, thereby promoting wound healing [99]. Similarly, Zhu et al. reported that near-infrared light exposure could enhance the antibacterial activity of Ti3C2Tx and Ag/Ti3C2Tx. And the Ag/Ti3C2Tx exhibited synergistic antibacterial mode to inhibit bacteria and accelerate wound healing under near-infrared light exposure (Fig. 8) [100]. Their high photothermal conversion efficiency generates localized heat upon light irradiation, enhancing bacterial inactivation and promoting healing [101]. Microneedles (MNs) offer enhanced drug delivery, minimal invasion, and improved permeability, significantly accelerating wound healing in diabetic foot ulcers. Shao et al. designed a MXene and spidroin-incorporated microneedle scaffold with photothermal responsive and self-healing properties. MXenes had excellent electrical and photothermal properties to sensitively monitor wound movement and control drug release under near-infrared irradiation. In vivo experiments also confirmed their enhanced wound healing ability (Fig. 8) [102].

In addition, the photothermal effect of MXene can also regulate the properties or control the loaded drugs release to achieve precise regulation of different bio-substances in composite materials. They can be regulated by the local precise temporal and spatial control [103]. Wang et al. developed a multifunctional membrane through loaded a chitosan-MXene suspension on PVDF membrane. This composite material significantly accelerated infected wound healing (Fig. 8) [104]. Zhang S et al. fabricated a titanium carbide (MXene)/zeolite imidazole framework-8 (ZIF-8)/

polylactic acid (PLA) composite membrane (MZ-8/PLA) as a multifunctional therapeutic platform. The photothermal (PTT) convention efficiency and bactericidal rate were 80.5%, more than 99.0%, respectively. This composite accelerated wound healing even infected with drug resistant bacterial infection(Fig. 8) [105]. And MXene@AgNPs hydrogel with multi-stimulus repose activities was designed to precisely control release of AgNPs. And it also significantly reduced the cytotoxicity. The animal experiments confirmed the enhanced wound healing ability [63].

Accordingly, the photothermal effect of MXenes holds promising potential in wound healing, as it enables efficient conversion of light energy into heat, promoting localized blood circulation, accelerating cell proliferation, and enhancing tissue regeneration, thereby expediting the healing process. Future research aims to optimize MXene formulations and explore their integration with advanced wound dressings for more effective and personalized wound management.

2.9 Hemostatic ability

Effective and rapid hemostasis is crucial for wound healing through reducing blood loss and infection rate [106]. Wu et al. reported that rapid hemostasis is important at the early stage of skin injury to prevent local infection [107]. However, effective wound hemostasis and healing promotion properties remain a major challenge in the design of hemostatic materials.

MXenes exhibit significant potential in promoting hemostasis through two main mechanisms. They have higher porous structure for absorption and entrapment of blood components. MXene-based NPs were embedded into a chitin sponge (CH) network to achieve hemostatic capability and antibacterial ability. And NIR was also used to increase the antibacterial ability to 100% because of the synergistic effect of MXene capturing and the photothermal effect. In vivo experiments had confirmed the excellent wound closure rate [81]. Huang et al. developed a hemostatic sponge (CMNCu) consisting of chitosan, aminated MXene, and copper ions. The internal topological point-line-surface interaction endowed CMNCu with highly effective antibacterial activity and long-lasting controlled release ability (Fig. 9) [108].

On the other hand, the surface charge can also activate platelet aggregation and stable clot formation [109, 110]. Surface modifications are employed to enhance hemostatic properties through improving the adhesion of platelets and the activation of clotting factors [111]. Li et al. developed a MXene@polydopamine (MXene@PDA)-decorated chitosan non-woven fabric (M-CNF) hemostatic dressing. The decoration of MXene@polydopamine (MXene@PDA) endowed them with excellent blood-clotting performance and blood cell and platelet adhesion ability in vivo and in vitro (Fig. 9) [112]. Zhou et al. fabricated an HPEM hydrogel for methicillin-resistant Staphylococcus aureus (MRSA)-infected wound healing. It was composed of the poly(glycerol-ethylenimine), Ti3C2Tx MXene@polydopamine (MXene@PDA) nanosheets, and oxidized hyaluronic acid (HCHO). HPEM hydrogel achieves rapid hemostatic capability through promoting rapid blood clotting (Fig. 9) [113]. Similarly, polydopamine-coated MXene was also used to decorate the Ag3PO4 bioheterojunctions to achieve the ability of hemostasis and promote epithelialization [114].

Overly, MXenes exhibit promising potential in wound hemostasis due to their unique two-dimensional structure, high surface area, and excellent biocompatibility, enabling rapid clotting and sealing of wounds. Future research endeavors are anticipated to further unravel their mechanisms of action, optimize surface modifications for enhanced efficacy and safety, and explore their clinical applications, thereby revolutionizing the field of trauma care and emergency hemostasis.

In conclusion, while the potential of MXenes in diabetic foot wound healing is promising, further research is needed to fully understand their mechanisms of action and optimize their use in clinical settings. Additionally, the safety and biocompatibility of MXenes must be thoroughly evaluated before they can be considered for widespread use.

3 Potential applicability of MXenes-based therapeutic strategies in diabetic foot management

Currently, various novel MXenes-based composite materials have been designed for diabetic foot management. In this section, we will provide the potential application of MXenes-based therapeutic strategies in diabetes foot from four aspects, including wound dressings, drug delivery systems, tissue engineering, and biosensing for Diabetic foot.

3.1 Wound dressings

To achieve a faster diabetic foot wound healing, various wound dressings (such as hydrogels, gelatin sponges, fiber dressings, and film dressings), even packed with bioactive agents, are innovated. Recently, bioactive nanoparticles showcase their versatility in enhancing wound healing, including antibacterial activity, tissue regeneration, and targeted drug delivery, revolutionizing traditional wound care strategies. They can create a moist wound environment and ensure gas exchange for wound healing [115].

Of them, the exploration of MXenes in wound dressing applications has garnered significant attention due to their

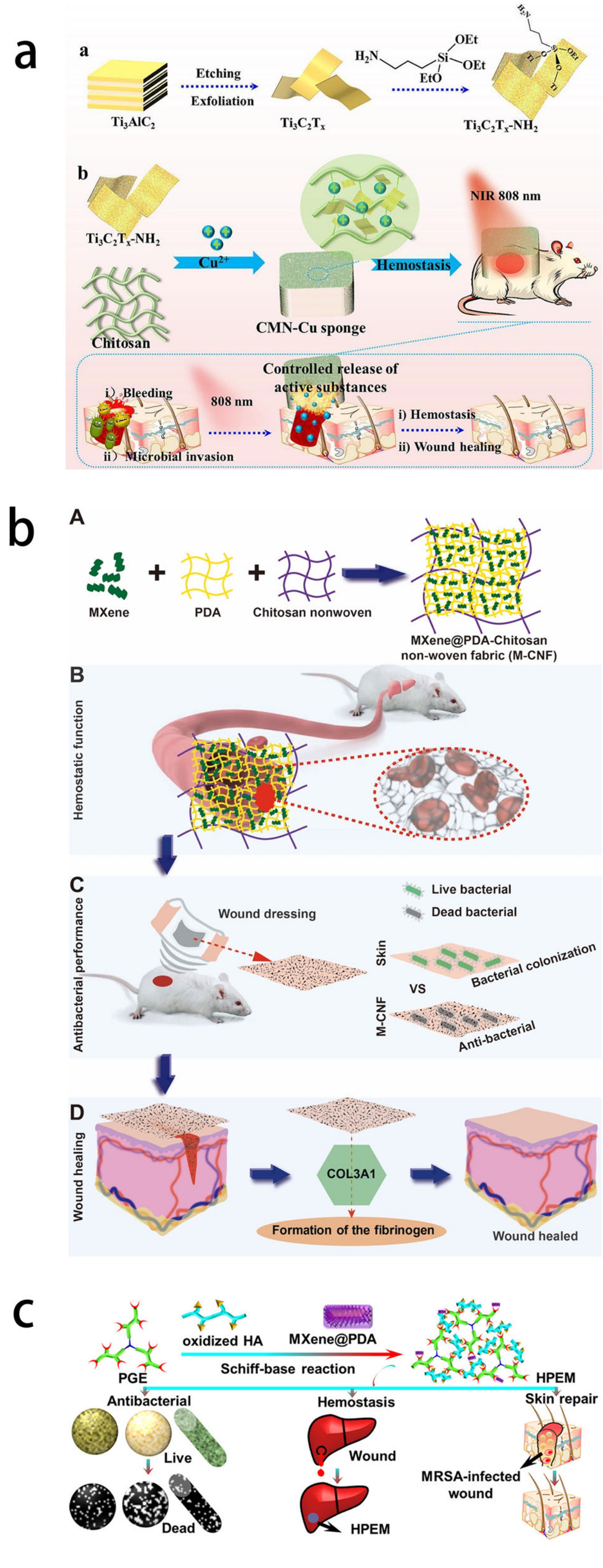
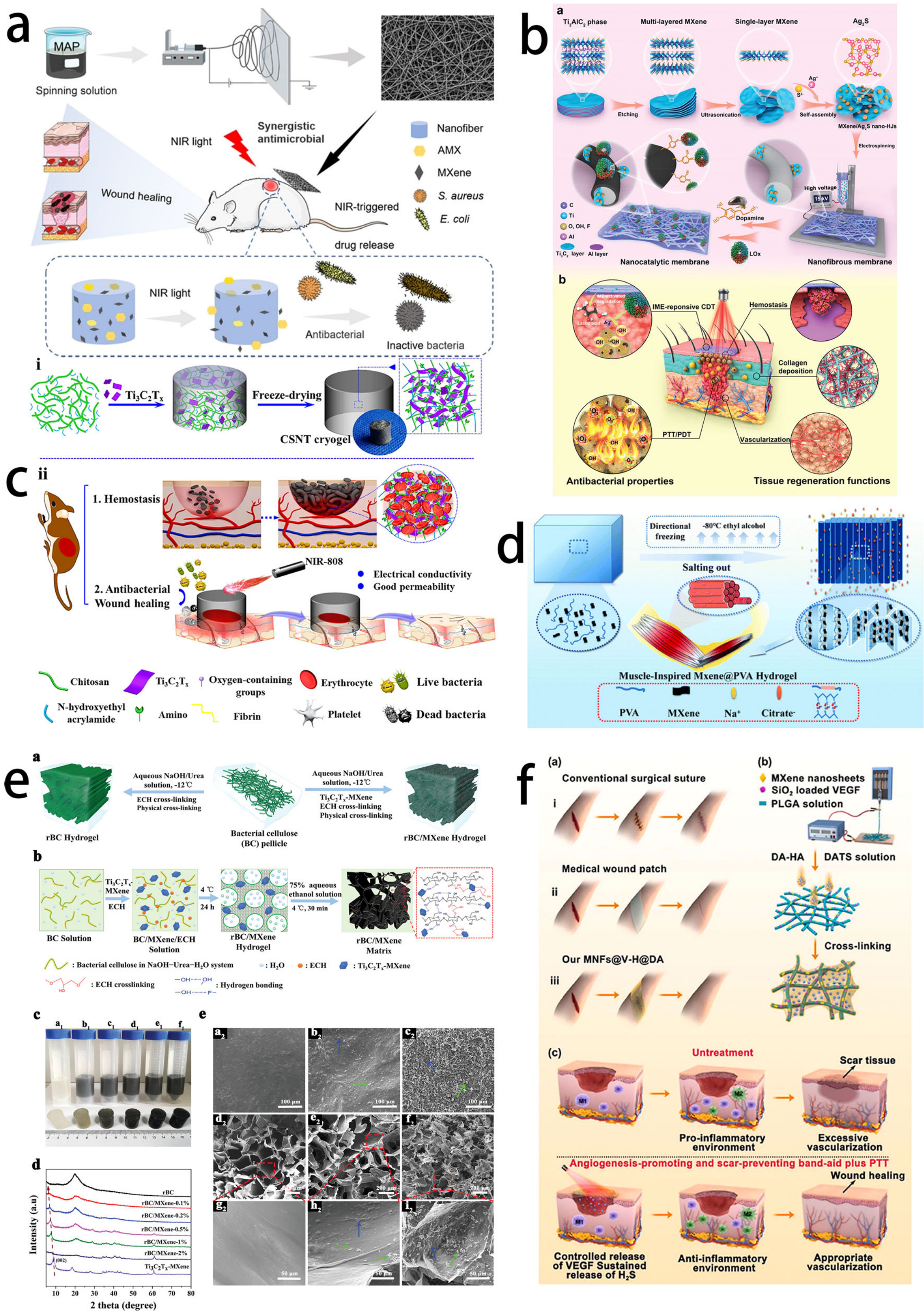


Fig. 9 Hemostatic ability of MXenes in Diabetic Foot Wound Healing. **a** A hemostatic sponge CMNCu exhibited highly effective antibacterial activity and long-lasting controlled release ability. Reproduced with permission [108] Copyright 2024 Published by Elsevier B.V. **b** MXene@PDA-decorated chitosan non-woven fabric (M-CNF) hemostatic dressing had excellent blood-clotting performance and blood cell and platelet adhesion ability. Reproduced with permission [112]. Copyright 2022 Published by Elsevier B.V. **c** HPEM hydrogel achieves rapid hemostatic capability through promoting rapid blood clotting. Reproduced with permission [113]. Copyright 2021 American Chemical Society

exceptional properties that hold immense potential to revolutionize wound healing processes, offering a promising alternative to conventional dressings. These new composite dressings simultaneously have the inherent properties of MXene and effective ingredients of other traditional excipients to achieve wound healing. MXenes have good antibacterial activities due to their oxidative stress and mechanical damage. Fiber dressings can create a relatively dry microenvironment for wound repair by absorbing the wound exudation [116]. Chitosan nanofiber loaded with MXene exhibited broad spectrum antibacterial effect and higher growth inhibition of bacteria [117]. Xu et al. developed a multimodal antibacterial nanofibrous membrane (MXene-AMX-PVA nanofibrous membrane), consists of amoxicillin (AMX), MXene, and polyvinyl alcohol (PVA). PVA matrix could control the release of AMX, while the local hyperthermia from MXene promotes the AMX release under near-infrared laser irradiation. These mechanisms synergistically resist bacteria and promoted wound healing [82]. Electrospinning is a well-established technique to architect various three-dimensional network structures for biomedical applications. MXene-decorated electrospun fibers are another promising wound healing method due to their good control ability of wound hygroscopic balance. Zhou et al. developed a novel infectious microenvironment (IME)-activated nanocatalytic membrane (P-MX/AS@LOx) by electrostatic spinning. It accelerated the skin wounds healing through massacring bacteria, stopping bleeding, and boosting epithelialization/collagen deposition (Fig. 10) [118]. In addition to antibacterial properties, hemostasis is also an important step for novel wound dressings. Li et al. fabricated a composite sponge by embedding MXene-based nanomaterials into a chitin sponge (CH) network. This composite sponge exhibited an excellent hemostatic and antibacterial activity for wound healing [81]. Wu et al. developed a hemostatic antibacterial chitosan/N-hydroxyethyl acrylamide (NHEMAA)/$Ti_3C_2T_x$ (CSNT) composite cryogel. It was water/blood-triggered shape memory sponge and exerted pressure on the wound after contacting with blood. Ti3C2Tx was added to enhance the hemostatic and antibacterial properties with high biocompatibility and safety (Fig. 10) [119]. This composite efficiently induced the coagulation for managing deep noncompressible wounds.

And several studies have demonstrated the potential of MXene-based hydrogels in diabetic foot wound healing. The


a
MAP
Spinning solution
NIR light
Synergistic antimicrobial
Nanofiber
AMX
MXene
S. aureus
E. coli
Wound healing
NIR-triggered
drug release
NIR light
Antibacterial
Inactive bacteria
b
a
Ti_3AlC_2 phase
Multi-layered MXene
Single-layer MXene
Ag_2S
Etching
Ultrasonication
Self-assembly
MXene/Ag_2S nano-HJs
Electrospinning
High voltage
Dopamine
LOx
Nanocatalytic membrane
Nanofibrous membrane
b
IME-reponsive CDT
Hemostasis
Collagen deposition
PTT/PDT
Vascularization
Antibacterial properties
Tissue regeneration functions
c
i
$Ti_3C_2T_x$
Freeze-drying
CSNT cryogel
ii
1. Hemostasis
NIR-808
Electrical conductivity
Good permeability
2. Antibacterial Wound healing
Chitosan
$Ti_3C_2T_x$
Oxygen-containing groups
Erythrocyte
Live bacteria
N-hydroxyethyl acrylamide
Amino
Fibrin
Platelet
Dead bacteria
d
Directional freezing
-80°C ethyl alcohol
Salting out
Muscle-Inspired Mxene@PVA Hydrogel
PVA
MXene
Na^+
Citrate-
e
a
Aqueous NaOH/Urea solution, -12℃
ECH cross-linking
Physical cross-linking
Aqueous NaOH/Urea solution, -12℃
$Ti_3C_2T_x$-MXene
ECH cross-linking
Physical cross-linking
rBC Hydrogel
Bacterial cellulose (BC) pellicle
rBC/MXene Hydrogel
b
$Ti_3C_2T_x$ MXene
ECH
4 ℃
24 h
75% aqueous ethanol solution
4 ℃, 30 min
BC Solution
BC/MXene/ECH Solution
rBC/MXene Hydrogel
rBC/MXene Matrix
: Bacterial cellulose in NaOH−Urea−H_2O system
: H_2O
: ECH
: $Ti_3C_2T_x$-MXene
: ECH crosslinking
: Hydrogen bonding
c
d
rBC
rBC/MXene-0.1%
rBC/MXene-0.2%
rBC/MXene-0.5%
rBC/MXene-1%
rBC/MXene-2%
$Ti_3C_2T_x$-MXene
(002)
Intensity (a.u)
2 theta (degree)
e
100 μm
50 μm
f
(a)
Conventional surgical suture
i
Medical wound patch
ii
Our MNFs@V-H@DA
iii
(b)
MXene nanosheets
SiO_2 loaded VEGF
PLGA solution
DA-HA
DATS solution
Cross-linking
(c)
Untreatment
Scar tissue
Pro-inflammatory environment
Excessive vascularization
Angiogenesis-promoting and scar-preventing band-aid plus PTT
Wound healing
Controlled release of VEGF Sustained release of H_2S
Anti-inflammatory environment
Appropriate vascularization

◀ **Fig. 10** MXenes-based Wound dressings. **a** MXene-AMX-PVA nanofibrous membrane synergistically resists bacteria and promotes wound healing. Reproduced with permission [82]. Copyright 2021 Elsevier B.V. **b** P-MX/AS@Lox by electrostatic spinning accelerated the skin wounds healing through massacring bacteria, stopping bleeding, and boosting epithelialization/collagen deposition. Reproduced with permission [118]. Copyright 2022 Wiley-VCH Verlag. **c** A chitosan/NHEMAA/Ti3C2Tx composite cryogel exhibited enhanced hemostatic and antibacterial properties. Reproduced with permission [119]. Copyright 2024 Published by Elsevier Ltd. **d** MXene@PVA hydrogels exhibited broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria through PTT to achieve wound healing. Reproduced with permission [120]. Copyright 2022 American Chemical Society. **e** A composite hydrogel with rBC and Ti3C2Tx exhibited a high electrical conductivity to achieve wound healing under external electrical stimulation. Reproduced with permission [122]. Copyright 2020 John Wiley and Sons Ltd. **f** NIR-responsive MNFs@V-H@DA hydrogel was fabricated to induce cell growth and blood vessel formation to achieve scar-free wound healing. Reproduced with permission [124]. Copyright 2022 KeAi Communications Co

results showed significantly faster wound healing compared to controls, with improved tissue regeneration and reduced inflammation. Li et al. designed an anisotropic MXene@PVA hydrogels with excellent mechanical properties. It exhibited broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria through photothermal therapy (PTT) to achieve wound healing (Fig. 10) [120]. Hu et al. designed MXene-based 'Shape memory'' hydrogels, consisting of MXene, gelatin, poly (ethylene glycol) diacrylate (PEGDA), and N,N'-methylenebis(acrylamide) (HEAA). They have double networks: one was the hydrogen bond, and the other was the crosslink reaction of PEGDA. The ability to promote wound healing had been confirmed in mouse experiments [121]. Zhou L et al. developed multifunctional scaffolds (HPEM) through the reaction between the poly(-glycerol-ethylenimine), Ti3C2Tx MXene@polydopamine (MXene@PDA) nanosheets, and oxidized hyaluronic acid (HCHO). HPEM scaffold exhibited antibacterial, hemostatic, tissue adhesion, and electrical conductivity properties simultaneously to enhance multidrug-resistant bacteria-infected wound healing [113]. Electrical stimulation or physiological electrical signals can effectively promote wound healing. Mao L et al. designed a composite hydrogel with regenerated bacterial cellulose (rBC) and MXene (Ti3C2Tx). This hydrogel dressing exhibits a high electrical conductivity to achieve wound healing under external electrical stimulation. the proliferation activity of NIH3T3 cells was enhanced after coupling with electrical stimulation (Fig. 10) [122]. MXene-assisted electrical stimulation therapy provides a promising new direction for wound treatment.

Considering the internal and external factors affecting skin wound healing, various bioactive substances are added into wound dressings to achieve different biological functions [123]. A novel NIR-responsive hydrogel (MNFs@V-H@DA) was fabricated, consisting of MXene-loaded nanofibers (MNFs), vascular endothelial growth factor (VEGF), and a H2S donor (diallyl trisulfide, DATS). This composite could induce cell growth and blood vessel formation to achieve scar-free wound healing (Fig. 10) [124]. Vitamin E was embedded into temperature-responsive MXene nanoribbon to achieve reasonable release of through increased temperature under NIR irradiation. This dressing effectively improved wound healing [125].

In summary, numerous potential directions for research and development of MXenes-based wound dressing do exist. Researchers are continually exploring ways to enhance these properties, such as through surface modifications or the development of composite materials that combine MXenes with other bioactive agents. This could lead to the creation of advanced wound dressings that not only provide a moist healing environment but also actively fight infection and promote tissue repair. And MXenes' unique electrical conductivity could be leveraged for the development of smart wound dressings that can monitor wound healing progress in real-time. Furthermore, MXenes may also find applications in combination therapies for diabetic foot ulcers.

3.2 Drug delivery systems

Local drug therapy is the most commonly used method for wound treatment. However, a reasonable drug delivery system based on different morphological designs can better prolong the drug action time and efficacy, and reduce the occurrence of adverse reactions [126]. The unique properties of MXenes make them attractive carriers for targeted drug delivery. They can be loaded with antibiotics, growth factors, or other therapeutic agents and released in a controlled manner to the wound site, enhancing treatment efficacy and reducing side effects. MXenes have been regarded as attractive candidates to enable sustained drug release and targeted drug delivery [127]. For example, Zhang WJ et al. developed a ROS-cleavable nanoparticle system (MXene-TK-DOX@PDA) to deliver Doxorubicin (DOX), which had ROS-responsive and pH-responsive release performance. In addition, it also had broad spectrum antibacterial ability [128].

MXenes can also be embedded in other delivery carriers, such as hydrogels and microneedles. MXene-based hydrogels can be developed to retain moist microenvironment for re-epithelialization and control the release of loading drugs [129]. And it also exhibits enhanced mechanical properties [130]. For example, inspired by natural skin, Luo et al. designed a tissue-nanoengineered hyperbranched polymer-based multifunctional hydrogel (CHHCMgel), which possessed adjustable mechanical and bioelectroactive characteristics, fast gelation time, self-healing ability, and repeatable adhesion. It could accelerate wound healing through comprehensive therapeutic effects and simultaneously monitoring real-time large-scale human motion (Fig. 11) [131]. And microneedle systems are also designed to be promising drug delivery vehicles. They can also deliver various compounds to enhance angiogenesis and tissue regeneration. MXenes were embedded in microneedles to control the sustained release of angiogenic factors under NIR irradiation [132]. MN-PGA-MXene-Gox was developed to regulate in situ hyperglycemic microenvironments, which was a poly (γ-glutamic acid) (γ-PGA)-based microneedle (MN) patch encapsulated with glucose oxidase (GOx)-loaded Ti3C2 MXene nanosheets (MXene). Gox could lowered local glucose and pH by oxidizing glucose, while MXene ensured its prolonged release. This multifunctional microneedle patch provided a novel approach for accelerating diabetic wound healing (Fig. 11)

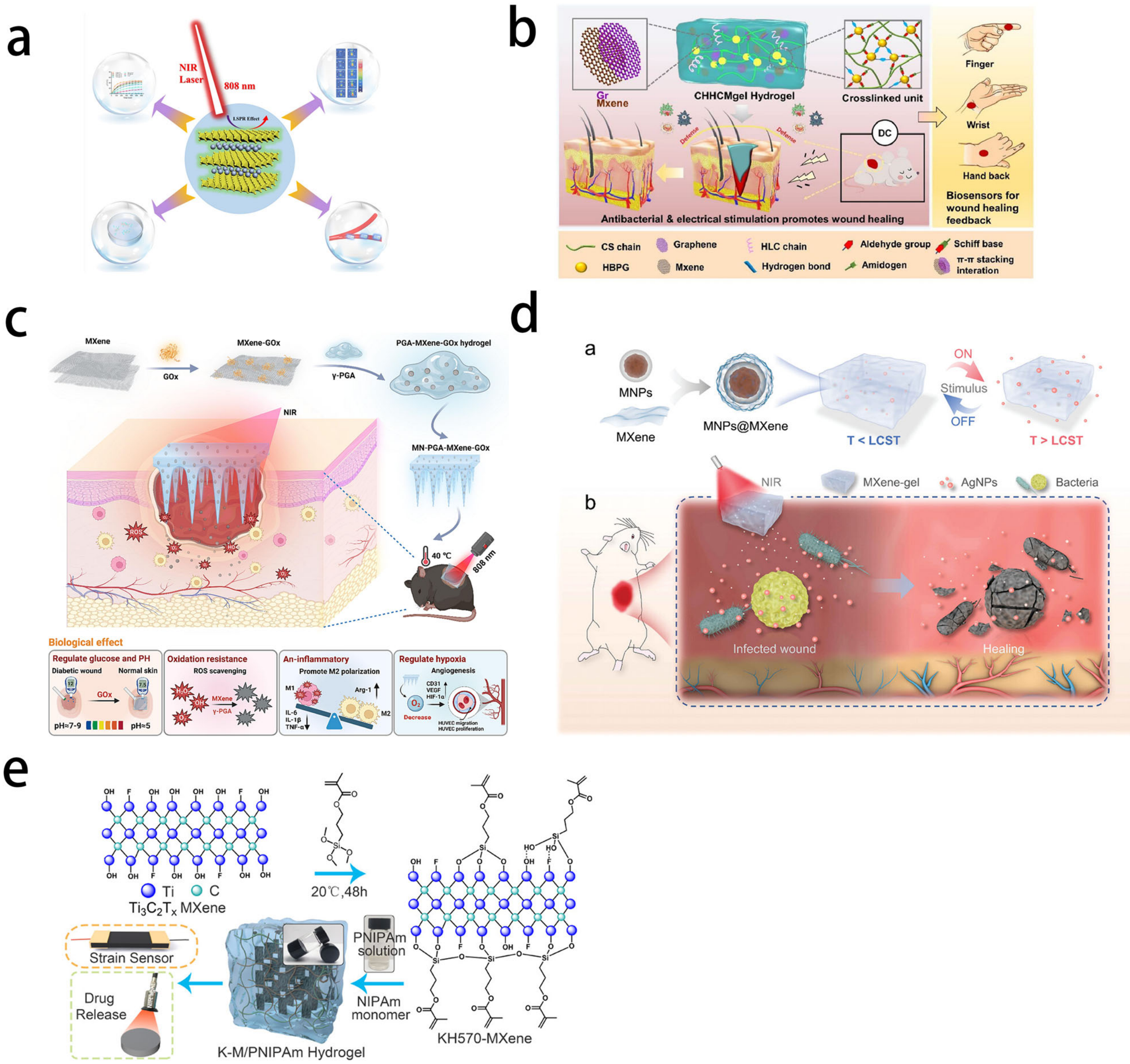


Fig. 11 MXenes-based Drug Delivery Systems. **a** MXene-TK-DOX@PDA could deliver Doxorubicin (DOX), which had ROS-responsive and pH-responsive release performance. Reproduced with permission [128]. Copyright 2022 MDPI. **b** CHHCMgel could accelerate wound healing through comprehensive therapeutic effects and simultaneously monitoring real-time large-scale human motion. Reproduced with permission [131]. Copyright 2022 Elsevier BV. **c** MN-PGA-MXene-Gox was developed to regulate in situ hyperglycemic microenvironments for accelerating diabetic wound healing. Reproduced with permission [133]. Copyright 2024 Elsevier. **d** A 2D MXene-based hydrogel system achieved controllable drug delivery ability and promoted the wound healing with multiple response capabilities. Reproduced with permission [63]. Copyright 2021 Wiley-VCH GmbH. **e** K-M/PNIPAm hydrogel had a high strain sensitivity and NIR-controlled drug release functions to achieve on-demand drug release. Reproduced with permission [136]. Copyright 2021 American Chemical Society

[133]. Sun et al. developed novel MXene-integrated microneedle patches with adenosine encapsulation to achieve wound healing. The photothermal conversion capacity of MXene could achieve the release of loaded adenosine under NIR irradiation. The microneedle patches efficiently enhancing angiogenesis and promoted wound healing [134]. Inspired by shark tooth, biomimetic microneedle patch was designed by replicating laser-engraved negative molds to achieve well tissue adhesion ability [135].

Recently, stimuli-responsive hydrogel systems have emerged as a hotspot recently. Yang X et al. developed a 2D MXene-based hydrogel system, consisting of MXene-wrapped magnetic colloids and poly (N-isopropyl acrylamide)-alginate dual-network hydrogels, to achieve controllable drug delivery ability. It promoted the wound healing and reduced the occurrence of adverse reactions with multiple response capability [63]. Hao et al. fabricated a smart hydrogel dressing (K-M/PNIPAm hydrogel) based on conductive MXene nanosheets and a temperature-sensitive PNIPAm polymer. γ-Methacryloxypropyltrimethoxysilane (KH570). It had a high strain sensitivity and NIR-controlled drug release functions to achieve on-demand drug release (Fig. 11) [136].

In summary, the future of MXenes in drug delivery is characterized by innovation and multidisciplinary collaboration, with numerous potential areas of development that could lead to more effective, personalized, and safe treatments for a wide range of diseases. The specific forms of drug delivery can be summarized as follows: the development of targeted drug delivery systems through surface modification, combining MXenes with other bioactive agents or nanomaterials, biosensors monitoring drug levels, and advanced imaging techniques for monitoring drug distribution and efficacy.

3.3 Tissue engineering

MXenes have garnered significant attention in the field of wound tissue regeneration due to their exceptional properties, such as high conductivity, hydrophilicity, biocompatibility, and antibacterial activity. These materials have demonstrated promising potential in enhancing wound healing processes by facilitating cell proliferation, angiogenesis, and reducing infection risk. Meanwhile, the ability of MXenes to adhere to tissues and promote cell adhesion and proliferation makes them potential candidates for tissue engineering applications.

MXenes have shown potential in tissue engineering by providing structural support for cell growth and differentiation. Their electrical conductivity can stimulate cellular activities, promoting the formation of functional tissues such as skin, nerve, and blood vessels, which are crucial for the complete recovery of diabetic foot ulcers [137]. Zheng et al. fabricated FOM scaffolds, consisting of Ti3C2Tx MXene, antioxidant CeO_2, polyethyleneimine-grafted polyethylene ions F127 (F127-PEI), and the dynamics of oxidized sodium alginate (OSA). The wound healing ability was also confirmed through promoting granulation tissue formation, fibroblast proliferation, and re-epithelialization (Fig. 12) [138]. MXenes-based composites manifest with good mechanical strength. And they also deliver electrical signals to induce tissue regeneration for wound healing [20]. A hydrogel-based bionic skin was designed, consisting of chitosan, human-like collagen, hyperbranched polyglycidyl ether, Ti3C2Tx MXene, and graphene nanosheets. This bionic skin could inhibit bacteria in infected wounds and monitor therapeutic effects and human motion by detecting changes in electrical resistance. With the addition of electrical stimulation, the bionic skin could effectively transmit exogenous electrical signals at the wound site, promoting wound closure by accelerating fibroblast and keratinocyte growth, collagen and granulation tissue formation, and re-epithelization [139].

MXenes-based wound dressings leverage their high surface area and tunable surface chemistry to enhance wound healing. They can act as scaffolds for cell growth, promote angiogenesis, and facilitate the absorption of exudates, thereby maintaining a moist environment conducive to healing [140]. The multifunctional MXene-based hydrogels exhibit tissue adhesion, self-healing, and injectability, allowing for easy application and adaptability to irregular wound surfaces. These properties, combined with the photothermal effect, significantly promote the proliferation and migration of human umbilical vein endothelial cells (HUVECs), facilitating angiogenesis and wound closure [141]. Additionally, their electrical conductivity can be harnessed for electrical stimulation therapies to accelerate healing processes. Anisotropic MXene@PVA hydrogels were designed to prevent infection and promote wound healing. They exhibit excellent mechanical properties, photothermal effects, and broad-spectrum antibacterial activity [120].

The surface of MXenes is terminated with functional groups such as hydroxyl, oxygen, or fluorine, which can facilitate interactions with biological tissues. The high surface energy and chemical reactivity of MXenes enable them to exhibit broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as some fungi. This property is particularly valuable in diabetic foot ulcers, where infections are a major complication [142]. And their surface chemistry can be tailored through functionalization with various groups (e.g., -OH, -F, -O), offering versatility in designing materials for specific biomedical applications [143]. The modification of functional groups on the surface exhibits great potential to achieve multi-function. Zhang et al. added lysozyme onto the

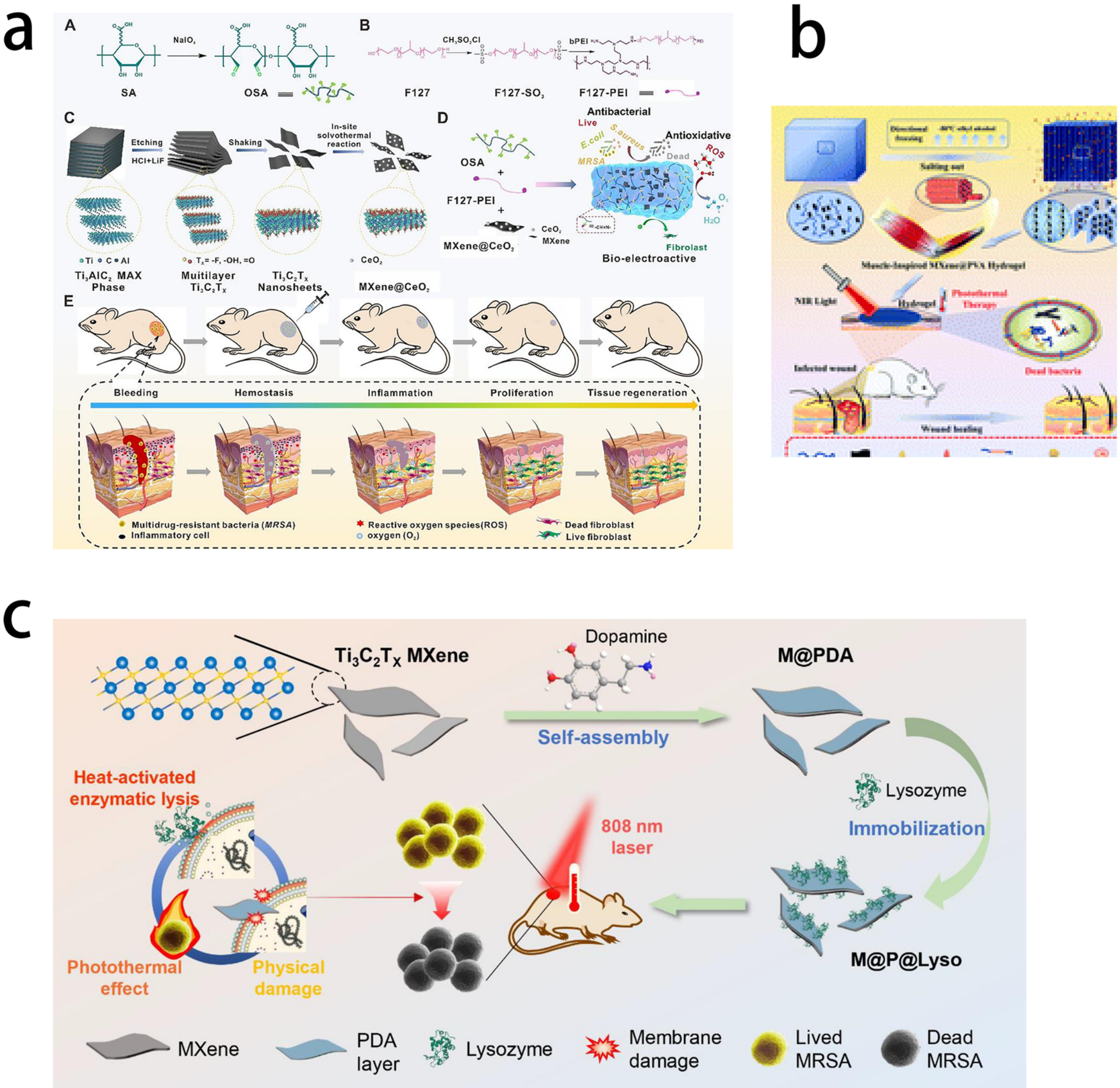
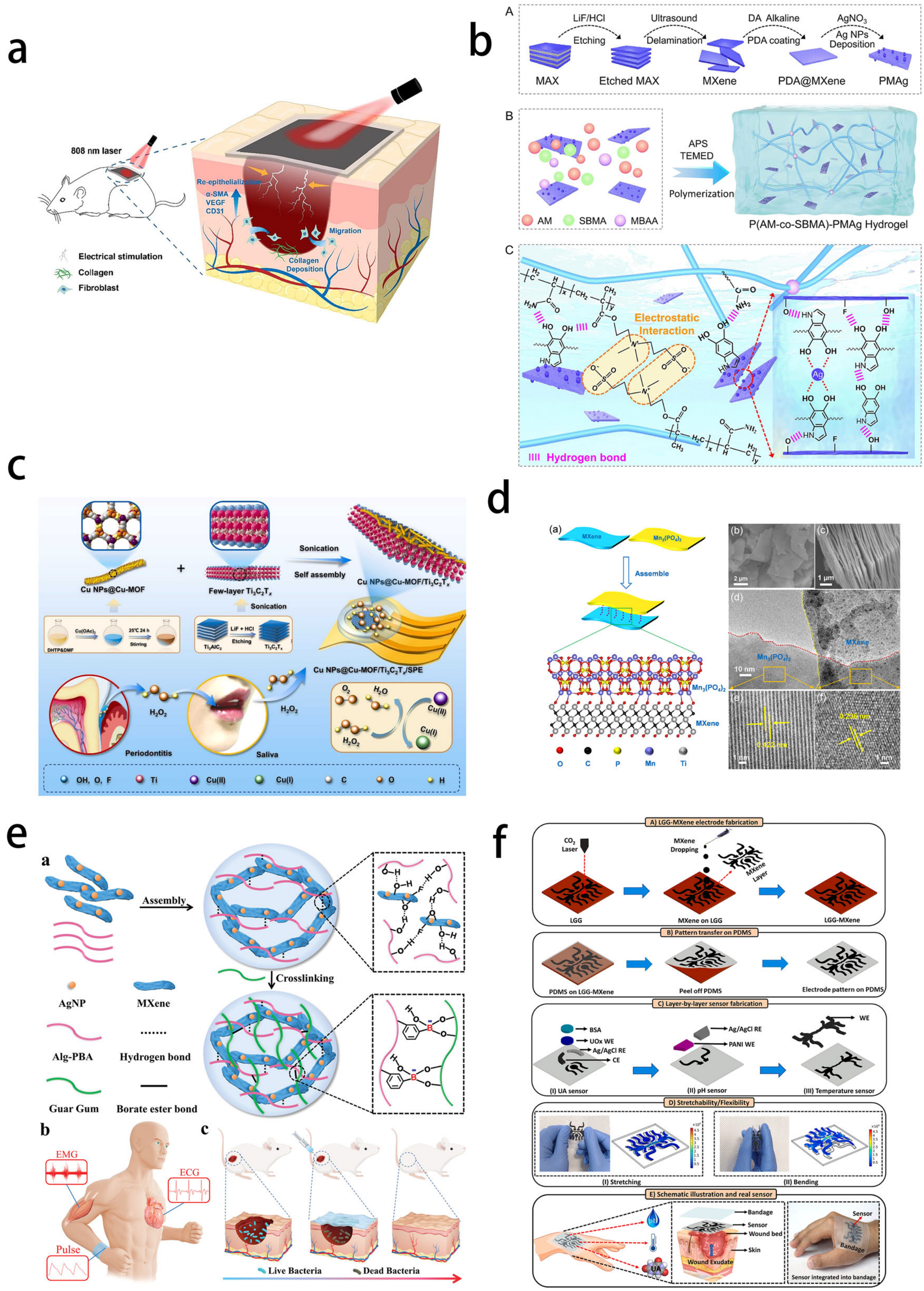


Fig. 12 Tissue Engineering. **a** Multifunctional scaffold based on MXene@CeO2 nanocomposites promoted granulation tissue formation, fibroblast proliferation, and re-epithelialization. Reproduced with permission [138]. Copyright 2021 Elsevier. **b** Anisotropic MXene@PVA hydrogels were designed to prevent infection and promote wound healing. They exhibit excellent mechanical properties, photothermal effects, and broad-spectrum antibacterial activity. Reproduced with permission [120]. Copyright 2022 American Chemical Society. **c** Zhang et al. added lysozyme onto the surface of Ti3C2TX MXene via intermolecular electrostatic affinity. The integrated nanoplatform exhibited outstandingly increased MRSA killing ability and promoted infected wound healing. Reproduced with permission [144]. Copyright 2023 Elsevier

surface of Ti3C2TX MXene via intermolecular electrostatic affinity. The integrated nanoplatform exhibited outstandingly increased MRSA killing ability and promoted infected wound healing (Fig. 12) [144]. And the surface modification also influences the biosafety. The oxidation of the functional groups on the surface could significantly increase the cytotoxicity and decrease the safe concentration. And the smaller size Ti3C2 exhibited higher inhibition on tumor cells through endocytosis and autophagy [145].

Current research focuses on developing MXene-based composites, including hydrogels and nanofibers, that can serve as innovative dressings for acute and chronic wounds. The unique physicochemical properties of MXenes enable them to act as both bioactive scaffolds and drug delivery systems, promoting faster and more effective tissue regeneration. Looking ahead, future directions involve optimizing synthesis methods to produce pure MXenes with controlled surface chemistries, exploring their mechanisms of action in wound healing, and conducting rigorous clinical trials to validate their safety and efficacy. The continued advancement of MXenes research promises to revolutionize the landscape of wound care and tissue engineering.



3.4 MXenes in biosensing for diabetic foot

Diabetic foot complications, including ulcerations, infections, and eventually amputations, are a major concern for diabetic patients. Early detection and continuous monitoring of relevant biomarkers can significantly improve the management of these complications. Biosensing technologies have emerged as promising non-invasive tools for

◀ **Fig. 13** MXenes in Biosensing for Diabetic Foot. **a** A single-electrode TENG skin patch (TESP) was designed to real-time monitor the physiological signals from body movement, but also generate an electric field to induce tissue regeneration. Reproduced with permission [149]. Copyright 2022 American Chemical Society. **b** A multifunctional electronic skin (E-skin) could detect various human motions with rapid sensitivity and responsiveness. Besides, it also accelerated diabetic wound healing under electrical stimulation. Reproduced with permission [151]. Copyright 2024 Elsevier Ltd. **c** A flexible electrochemical H2O2 sensor to distinguish infections, consist of copper nanoparticle-anchored copper-based metal-organic framework (Cu NPs@Cu-MOF) and titanium carbide nanosheets (Ti3C2Tx NSs). Reproduced with permission [158]. Copyright 2023 Elsevier. **d** Mn3(PO4)2/MXene sensing platform was designed to detect the level of O^{2}•− in infected wounds. Reproduced with permission [159]. Copyright 2021 Tsinghua University Press. **e** A flexible healable MXene hydrogel with high-performance epidermic sensor to monitor human movements and tiny electrophysiological signals. This flexible healable MXene hydrogel exhibited great potential in smart medical treatment, wearable electronics, personal health diagnosis, and wearable human-machine interaction. Reproduced with permission [161]. Copyright 2022 Wiley-VCH Verlag. **f** A smart flexible bandage with pH, uric acid, and temperature detection functions for chronic wound care management. This integrated multifunctional flexible bandage exhibited uric acid (UA), pH, and temperature monitoring abilities and significantly improved the therapeutic outcomes of chronic wounds. Reproduced with permission [162]. Copyright 2020 Elsevier B.V

monitoring various biomarkers associated with diabetic foot complications. They have shown promise in biosensing for early detection and management of diabetes-related complications, enabling timely interventions and better patient outcomes [146, 147].

Currently, various MXene-based sensors emerge and underwent investigation vigorously. They can effectively real-time quantitative monitor alterations based on the different physical, chemical, or biological signals [148]. MXenes can be used to develop biosensors for monitoring vascular health in diabetic patients, providing insights into blood flow and potential issues related to diabetic foot complications. For example, MXene-based sensors have been developed for monitoring biomarkers associated with diabetic foot infections and peripheral arterial disease [139]. These sensors offer high sensitivity and selectivity, enabling early intervention and improved patient outcomes. And a single-electrode TENG skin patch (TESP) was designed consist of MXene nanosheets and gelatin hydrogel. TESP could real-time monitor the physiological signals from body movement, but also generate an electric field to induce tissue regeneration. The combined effects could improve the healing rate of wounds by upregulating the expression of asmooth muscle actin (a-SMA) and vascular endothelial growth factor (VEGF) (Fig. 13) [149].

MXene-based biosensors can be used to monitor the progress of wound healing in diabetic foot ulcers, providing valuable information on the efficacy of treatment and the need for intervention. A stretchable, flexible, and breathable bandage with three layers was developed to for wounds monitoring and treatment. Firstly, the polylactic acid/polyvinyl pyrrolidone (PLAP) fiber film with Kirigami structure was developed as the middle layer by electrostatic spinning strategy. Ti3C2Tx was modified to the top layer of PLAP fiber film, while polyaniline (PANI) and Ag/AgCl-modified thermoplastic polyurethane (TPU) fiber membranes were affixed to the underside. The f-sensor at the bottom could detect real-time microenvironmental changes [150]. Flexible health management systems exhibit both health monitoring and wound healing capabilities. Thus, D Liu et al. designed a multifunctional electronic skin (E-skin) consisting of a surface-modified MXene nanocomposite (PMAg) with a P(AM-co-SBMA) matrix. It could detect various human motions with rapid sensitivity and responsiveness. Besides, it also accelerated diabetic wound healing under electrical stimulation (Fig. 13) [151].

The high conductivity and large surface area of MXenes make them ideal for developing sensitive biosensors capable of detecting low concentrations of biomarkers associated with diabetic foot complications. MXenes can serve as efficient transducers in biosensing systems, converting biological signals into measurable electrical signals. The MXene-based dressings can detect minor changes (including pH, temperature, and humidity) in the microenvironment and exhibit excellent sensitivity, which can be used in personalized wound care [152–154]. Surface modifications can enhance the selectivity of MXene-based biosensors, allowing for the specific detection of relevant biomarkers in complex biological samples. The unique surface chemistry of MXenes facilitates the immobilization of bioreceptors, enzymes, or other recognition elements, enhancing the sensitivity and stability of biosensors [155]. MXene-based biosensors can also be integrated with other drug delivery systems for real-time monitoring the healing process [156].

Bacterial culture in clinical application remains a cornerstone for identifying and diagnosing bacterial infections, guiding antibiotic therapy, and monitoring therapeutic responses. However, its time-consuming nature hinders rapid diagnosis and timely treatment of infections [157]. By detecting specific biomarkers associated with infections, MXene-based biosensors can facilitate early diagnosis and treatment of diabetic foot infections, reducing the risk of severe complications. K Wang et al. developed a flexible electrochemical H2O2 sensor to distinguish infections, consist of copper nanoparticle-anchored copper-based metal-organic framework (Cu NPs@Cu-MOF) and titanium carbide nanosheets (Ti3C2Tx NSs) (Fig. 13) [158]. Mn3(PO4)2/MXene sensing platform was designed to detect the level of $O_2^{\bullet-}$ in infected wounds (Fig. 13) [159]. Bacterial virulence factor detection is also needed to assist therapeutic strategies. Ti3C2Tx MXene was applied to design a battery-free, wireless, and wearable smart bandage through enhancing the sensitivity. in vivo experiments also confirmed its effectiveness for the management of the infected wound [160]. In future, the relationship between markers and infection degree is also needed to facilitate clinical management. In addition, the stability, repeatability, and reliability are also needed to be further confirmed.

Recently, MXenes-based wearable or implantable biosensing devices have been emerging for continuous monitoring of diabetic foot biomarkers, which has well flexibility and lightweight nature. These devices can provide real-time data on biomarker levels, enabling early detection of complications and timely interventions. Li et al. fabricated a flexible healable MXene hydrogel with high-performance epidermic sensor to monitor human movements and tiny electrophysiological signals. Antibacterial AgNPs/MXene nanosheets network was incorporated into hydrogel to achieve mechanical strength and antibacterial properties. And the supramolecular interaction endowed it with excellent self-healing capacity. This flexible healable MXene hydrogel exhibited great potential in smart medical treatment, wearable electronics, personal health diagnosis, and wearable human-machine interaction (Fig. 13) [161]. And simultaneous detection of multiple targets exhibits a promising potential to improve the accuracy of detection. Sharifuzzaman et al. designed a smart flexible bandage with pH, uric acid, and temperature detection functions for chronic wound care management. Firstly, an LGG-MXene hybrid scaffold, consist of three-dimensional (3D) porous laser-guided graphene (LGG) and 2D MXene nanosheets, was developed. It could significantly improve sheet resistance and mechanical properties of LGG sheets. Then, this hybrid scaffold was transferred onto PDMS with multifunctional sensors. This integrated multifunctional flexible bandage exhibited uric acid (UA), pH, and temperature monitoring abilities and significantly improved the therapeutic outcomes of chronic wounds (Fig. 13) [162].

In conclusion, MXenes-based biosensors, with their unique physicochemical properties, hold great potential for biosensing applications in diabetic foot management. Despite the promising potential, challenges such as improving large-scale production, reproducibility, biocompatibility, and reducing toxicity, and ensuring long-term stability of MXene-based biosensors need to be addressed. Future research should focus on creating hybrid MXene composites with materials like MOFs, QDs, or nanoparticles to enhance sensitivity and expand the range of detectable analytes.

4 Challenges and future perspectives

Diabetic foot continues to pose significant challenges in clinical medicine due to their chronic nature, inefficient epithelization, and impaired angiogenesis. Traditional treatments often struggle with transdermal drug delivery, resulting in low drug delivery rates and suboptimal healing outcomes. The preliminary results of MXenes in diabetic foot applications are exciting and promising due to unique physicochemical properties.

In this review, we comprehensively summary current knowledge, unique characteristics, and underlying mechanisms of MXenes in the context of diabetic foot management. And we also provide an overview of the potential application of MXenes-based therapeutic strategies in diabetes foot. They can serve as wound dressings, drug delivery systems, and biosensing for diabetic foot. More importantly, MXenes-based therapeutic strategies can be optimized with new functions through different engineering strategies. However, their application in diabetic foot treatment faces several challenges and requires further research to realize their full potential.

i. *Biocompatibility and Safety*

Although preliminary studies have demonstrated the biocompatibility of MXenes, more extensive research is needed to fully understand their long-term effects on cellular and tissue function, as well as their potential toxicity. This is crucial for safe clinical translation. The long-term safety and biocompatibility of MXenes in vivo need to be thoroughly evaluated. Future research should focus on optimizing MXene formulations, exploring new delivery mechanisms, and conducting large-scale clinical trials to validate the efficacy and safety of MXene-based therapies. The biodegradability of MXenes in biological environments needs to be evaluated to ensure their safe use in long-term applications.

ii. *Surface Functionalization and Stability*

The surface chemistry of MXenes plays a vital role in their interactions with biological systems. Optimizing MXenes' surface chemistry through innovative surface engineering strategies can enhance their biocompatibility, stability, and functionality. This includes the exploration of novel surface functional groups, coatings, and composites that can further improve their performance in diabetic foot treatment. However, maintaining their surface functional groups during processing and in vivo conditions remains a challenge.

Developing advanced characterization techniques and computational models will help gain deeper insights into MXenes' interactions with biological systems. This knowledge can guide the rational design of MXenes-based therapies tailored to specific therapeutic targets and patient populations. Surface modifications can enhance their stability and functionality, but optimizing these modifications for specific applications requires further investigation. The specificity and selectivity of drug delivery can also be enhanced through surface engineering of various stimuli-responsive polymers. And the development of composites with other biomaterials may also enhance these properties and tailor them to specific needs.

iii. *Mechanical Strength, Drug Loading and Release Kinetics*

MXenes-based devices, such as microneedles, require sufficient mechanical strength to penetrate the skin barrier without causing damage. Balancing this strength with flexibility and structural integrity during device fabrication and in vivo use is a significant challenge.

And efficient drug loading and controlled release kinetics are essential for effective transdermal drug delivery. MXenes' high surface area and tunable surface chemistry offer advantages, but optimizing the loading and release profiles for specific drugs and therapeutic targets requires careful engineering. Combining MXenes with other materials and technologies can create multifunctional drug delivery systems that address multiple aspects of diabetic foot healing. For example, integrating MXenes with hydrogels can provide a moist healing environment while enabling controlled drug release.

iv. *Scale-Up and Manufacturing*

Transitioning MXenes-based therapies from the laboratory to clinical practice requires overcoming challenges related to large-scale synthesis, purification, and manufacturing. Ensuring consistent quality and cost-effectiveness at industrial scales is essential for widespread adoption. Furthermore, the scalability and cost-effectiveness of MXene-based products must be addressed to ensure their widespread clinical adoption.

The complexity of diabetic foot management stems from the interplay of poor glycemic control, neuropathy, and peripheral vascular disease. Neuropathy can alter wound healing physiology due to impaired sensory feedback, while peripheral vascular disease reduces local blood flow and impairs tissue oxygenation. In such cases, the performance of MXenes in wound healing applications may be further compromised. However, tailored strategies combining MXenes with other therapeutic modalities (e.g., hyperbaric oxygen therapy, revascularization procedures) may still offer some benefits.

In addition, conducting rigorous preclinical and clinical studies is essential for validating the safety and efficacy of MXenes-based therapies in diabetic foot treatment. These studies should focus on identifying optimal dosing regimens, treatment durations, and patient populations most likely to benefit from these therapies. Currently, various MXene-based biomaterials have been developed with good prognosis. However, clinical transformation and application are still in infant. And the development of user-friendly, wearable, or implantable biosensing devices that integrate MXenes and provide accurate, real-time data is crucial for widespread adoption.

In summary, MXenes, with their unique properties and diverse functionalities, have demonstrated significant advantages and potential in diabetic foot management. From wound healing to biosensing, MXenes offer innovative solutions to address the challenges associated with this severe complication. Furthermore, MXenes, with their unique tissue adhesion and self-healing properties, hold great promise for biomedical applications, particularly in tissue engineering and the development of durable biomedical devices. This strategy will ultimately pave the way for innovative solutions in diabetic foot management. However, further research is needed to address challenges related to biodegradability, long-term effects, and property optimization before these materials can be safely and effectively translated into clinical practice. With continued research and development, future research should focus on overcoming these barriers and exploring novel MXenes-based approaches for personalized and precision medicine in diabetic foot care.

Data availability

The data is available on request from the authors.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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