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### Latest advances in MXene biosensors

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## PERSPECTIVE

## Latest advances in MXene biosensors

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## 1. Introduction

Since it was first discovered in 2011 by Scientists at Drexel University, MXenes [1], have become one of the largest families of two-dimensional (2D) materials, suitable for a variety of applications. MXenes are exfoliated from bulk crystal called MAX. The properties of exfoliated few-layer MXenes are very different from those in the multi-layer ones. Few-layer MXene has been reported to favor superior electrochemical properties due to its 2D layer structure and excellent ionic conductivity. However, the compact multilayer structure largely decreases these properties, showing decreased storage capacity and poor conductivity [2]. Unlike most 2D materials, MXenes present inherent good conductivity and excellent volume capacitors because they are made from the carbides and nitrides of transition metals like titanium. MXene have already been widely applied, in energy storage, polymer nanocomposite fillers, water purification, transparent optical conductive coatings, electromagnetic shielding/absorption, and electronic devices. In 2018, an aqueous deposition technique was developed to generate flexible MXene thin films that offered new potentials for fabricating flexible electronics [3]. Despite the intense application of MXene in electronics, it is not well developed for use in biological applications.

The goal of this mini-review is to summarize the most current advances and challenges of developing MXene-based biosensors, aiming to facilitate the fabrication of related devices and enable novel biosensing techniques. MXene have been recognized as a highly advanced biosensing platform because of the high metallic conductivity, excellent ion-transmission properties, good biocompatibility, large surface area and ease of functionalization [1, 4, 5]. However, they were not used in biosensing applications until 2015. Xu and his colleagues [6] began to introduce the two-dimensional (2D) materials into the area of biosensors for probing neural activities. They utilized ultrathin MXene micropatterns to develop a highly sensitive field-effect transistor (FET) biosensor for label-free probing of small molecules in typical biological environments and fast detection of action potentials in primary neurons. This work opens a new window for biosensing applications using MXene, enabling more scientists to realize that MXenes can be a promising candidate for developing biosensors due to their large surface area, excellent electrical properties and good biocompatibility. Since then, increasing numbers of researches have begun to immobilizing enzymes or biomaterials on the surface of MXene electrodes for sensing applications. For example, Wang and Zhu have developed a novel bio-similar MXene-based nanomaterial for the manufacture of mediator-free biosensors [7]. The sensing device shows a low detection limit of 20 nM and a linear range of 0.1–260  $\mu\text{M}$  for  $\text{H}_2\text{O}_2$ . In addition, galvanic glucose biosensors [8] and nitrite biosensors [9] based on MXene materials have also been reported. Therefore, MXene-based materials have been recognized to be suitable for enzyme binding and show great potential in biosensing applications. New analysis and findings in whole blood and wearable electrochemical biosensors has been studied. Novel development of dual-function MXene allows for simultaneous quantification of different target signals through one single device. MXene present a good radiometric sensing range, which greatly reduces signal drifting [10]. A novel stretchable, wearable and modular multifunctional biosensor is designed for durable and sensitive detection of biomarkers in sweat. The novel device is potentially used in noninvasive biomarker monitoring [11]. Another implemented

solid–liquid–air three-phase interface was designed and present superior sensing performance and stability [11]. These new analysis and findings further support MXene as potential materials.

Compared with other 2D nanomaterials, MXene materials present some unique advantages. First, MXene nanosheets present a large surface area and are rich in surface functional groups such as  $-O$ ,  $-OH$ , and  $-F$ , which makes them easier to be modulated to absorb biological materials and alter the conductive properties, thus be very flexible in sensing different biomaterials [12–15]. At the same time, because of the semi-conductive metallic properties with a proper bandgap, MXenes exhibit less current leakages in an off-state than graphene, which favors a higher detection sensitivity [6]. Until now, various MXene nanosheet-based electrochemical biosensors have been developed for detecting phenol [16], antibodies [17], functional enzymes [16], and electrochemical DNAs [18]. These sensors can be used for biomedical detection and environmental analysis. Different of surface chemical could be induced by different synthesis approaches, which would influence the properties of MXene. As noted, upon etching, surface terminations were created, such as  $-OH$ ,  $-O$  or  $-F$  groups. The multilayer terminations depend on the etching method, nature of elements. It is reported that HF etching method offer almost four times more  $-F$  termination than ones etched in  $HCl/LiF$  [19]. Fluorine-free MXenes can also be fabricated by the hydrothermal treatment in  $NaOH$  [20]. Different synthesis approaches could affect the sensing properties/potential on MXene-based biosensor.

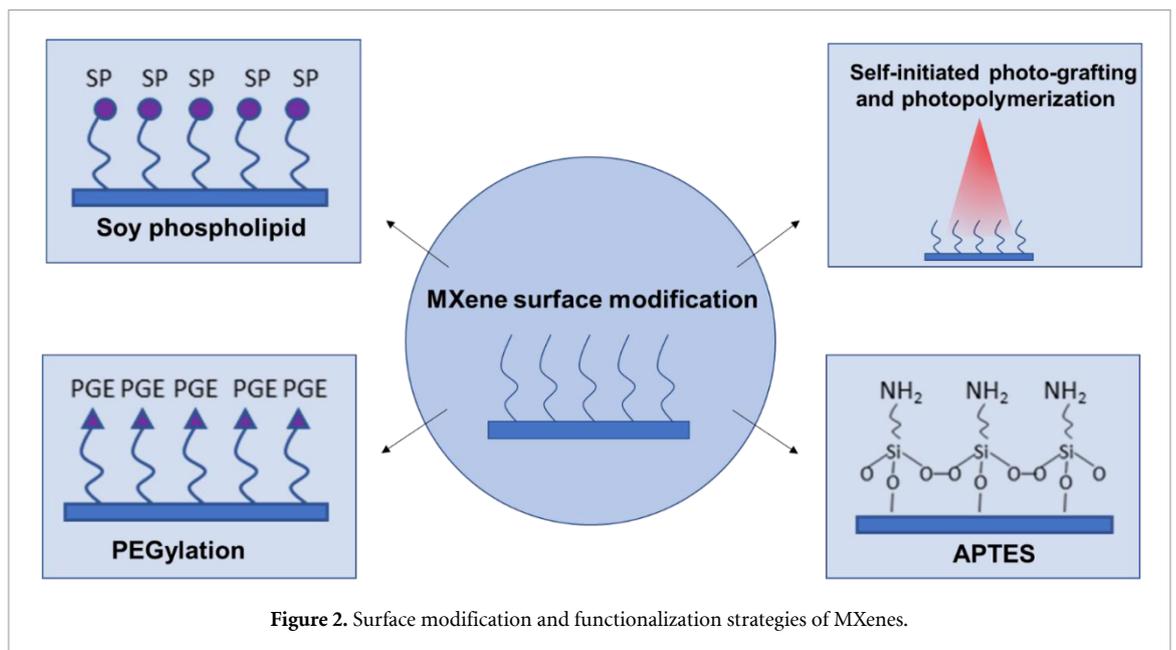
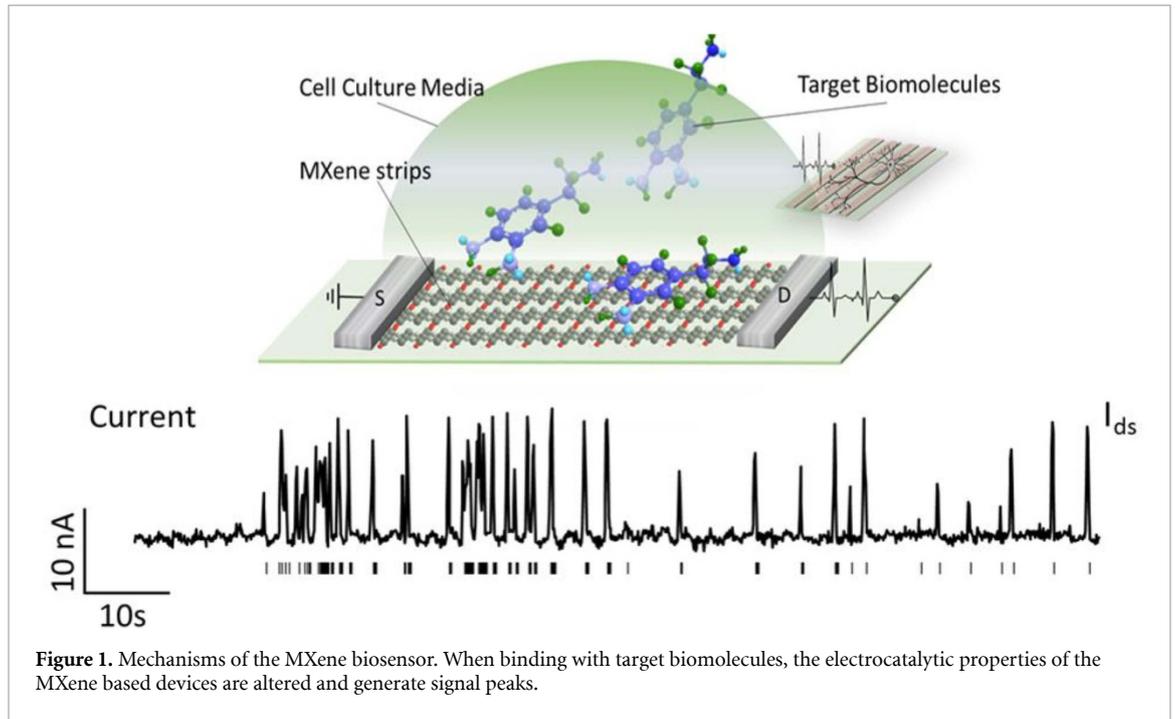
In this mini-review, we aim to provide some useful information for a better understanding and developing novel MXene-based biosensing techniques. The latest advances and challenges in MXene-based materials for biomedical applications are summarized and discussed. Surface modification and functionalization strategies for MXene-based materials were depicted to overcome some of the limitations of bare MXene-based biosensors. Several important applications of MXene biosensors, including protein sensors via physical adsorption, biomarker sensors via anchor antibodies, and E-DNA sensors with NDA nanostructures were highlighted. In addition, we will discuss the long-term toxicity and biocompatibility of MXene-based materials. At the end of this mini-review, the current challenges and prospects of MXene-based materials in biomedical applications are also discussed.

## 2. Surface modification and functionalization strategies of MXenes

As shown in figure 1, the mechanisms behind the MXene biosensor usually leverages the unique electrocatalytic properties of the MXene sheets according the concentration of the target signals [6]. When the biological targets bind to the MXene sheets, the electronic properties are altered, and current signal were changed. The 2D layer nanostructure create a high surface to entrap biological substances. When biological materials are immobilized by the active functional groups on surface of MXene nanocomposite, the electrocatalytic properties were altered and render a linear response. The MXene biosensor exhibit excellent stability, reproducibility and repeatability. Even though intensive research advances have been made on MXene-based sensors, these outstanding properties still cannot meet all the requirements of various applications. Therefore, surface modification and functionalization are necessary to improve their performance and endow new functions. Meanwhile, another potential problem is that non-covalent and physical adsorption interactions are not stable enough for some biomedical applications [21–25]. A possible solution could be to use the enriched functional groups on the surface of MXene-based materials to develop some novel and controllable binding on the surface to modify the surface properties.

Several surface modifications were illustrated as figure 2. One simple and easy polymerization method that can be used for surface modification on MXene is self-initiated photo-grafting and photopolymerization (SIPGP). This method is efficient and has several advantages over conventional polymerization methods, such as not demanding of an anchor layer, self-assembled monolayer (SAM) and initiator [26–28]. The whole process could be easily completed at room temperature with a direct brush under UV radiation. More importantly, SIPGP has been successfully applied to various substrates, including graphene [29], carbon nanotubes [30], silicon-based substrates [31], and diamond [32]. Another modification of MXene surface is using a nature polymer, soy phospholipid (SP) [33, 34], to enhance permeability, stable cycling, and retention. In addition, PEGylation of MXene [35] has been demonstrated to be an economical and effective way to improve the water dispersibility of MXene by electrostatic adsorption. A covalent strategy of modification was developed recently [17]. They employed (3-aminopropyl) triethoxysilane (APTES) as a bridge to conjugate PEG on the surface of MXene for biomedical applications. This modification provides two benefits: in one aspect, the bonding ability of APTES to hydroxyl render MXene the capability to bind to an amino group; on the other hand, the amino group could react with PEG and form PEGylated MXenes.

While some progress has been made in surface modification and biomedical applications of MXene-based materials, there are still a long way to go before some practical medical applications. For instance, in most biomedical applications, to improve the dispersity of the MXene-based materials, hydrophilic polymers are often used to modify MXene-based materials through non-covalent and physical



adsorption interactions, however, which are not stable enough in some extreme cases. For the case of using MXene for drug loading applications, most modification strategies of loading drugs on MXene are through non-covalent and physical adsorption interactions [26, 36, 37], which are not strong enough to maintain sufficient fastness in practical biomedical applications. When these unbonded drugs released from the materials could damage normal cells. Also, mostly the treatment efficiency is recognized by the concentration of effective drugs in cancer, therefore, controllable drug release is a key requirement in MXene-based drug delivery systems. As a consequence, proper surface modification strategies through covalent method on MXene to achieve better performance are expected in drug delivery applications and relate the functionalization of MXene to other bio sensing application as well.

### 3. MXene-based sensors via physical adsorption

Initially, Mxenes-based biosensors focused on using the advantages of using  $\text{Ti}_3\text{C}_2$ -MXene multilayer systems to immobilize electrochemically active proteins through physical adsorption, which was used to detect nitrites, pesticides, phenol and  $\text{H}_2\text{O}_2$  [9, 16, 38–40]. Liu Hui *et al* used MXene to immobilize hemoglobin

(Hb) to make mediator-free biosensors [9]. Two-dimensional multilayer MXene-  $\text{Ti}_3\text{C}_2$  nanomaterials can provide a protective microenvironment for proteins to maintain their activity and stability. More importantly, this unique structured MXene- $\text{Ti}_3\text{C}_2$  with high surface area has the function of concentrating the substrate, which results in the substrate being accessible by the immobilized enzyme in the nanomaterial [9]. Concentrated substrates and proteins on the electrode surface will increase the effective collision between them and improve the performance of the sensor. For the previously discussed reasons, the two-dimensionally layered MXene-based biosensor has a low detection limit for  $\text{NO}_2^-$  and a wide linear range. This study indicates that MXene- $\text{Ti}_3\text{C}_2$  can be used as biocompatible matrix for the enzyme immobilization and the construction of direct electrochemical biosensor and have great potential in  $\text{NO}_2^-$  analysis [9]. In addition, some scientists have also used MXene as a robust substrate to immobilize tyrosinase to achieve media-free detection of phenol [16]. The prepared tyrosinase biosensor has good sensitivity, repeatability and stability, low detection limit, wide linear range. The further validation of using the device for the rapid detection of phenol in tap water also showed satisfactory results. The MXene- $\text{Ti}_3\text{C}_2$ -based mediator-free biosensor provides a simple, sensitive, fast, and cost-effective method for detecting phenol in water. Overall, the MXene materials have been proven to be a promising candidate for enzyme immobilization and may have a wide range of potential applications in biomedical testing and environmental analysis. Although the sensing application of this physical adsorption method is effective, it does not make full use of the huge potential of MXenes' 2D nanosheet morphology to combine high density surface functional groups. Therefore, when detecting low concentrations of biomarkers, the sensing performance of physical adsorption methods is limited.

#### 4. MXene-based biomarker sensors via anchoring antibodies

Salama and colleagues reported about an aminosilane-functionalized MXene nanosheets which was capable to anchor antibodies and use them for electrochemical detection of cancer biomarkers [17]. In the paper, biological receptors were covalently immobilized on the amino groups which are chemically introduced to the surface of single/multilayer MXene ( $\text{Ti}_3\text{C}_2$ ). The high density of functional groups on the ultrathin 2D nanosheet of single/few layered  $\text{Ti}_3\text{C}_2$ -MXene largely offers improved biomolecule loading and faster access to analyte. In addition, biosensor performance would be largely enhanced due to the covalent immobilization of biological receptors (enzymes, DNA, proteins, etc), which could not only improve the uniformity and distribution, but also enables higher density of bound biomarkers. This biofunctionalized MXene device was demonstrated to present a wide linear detection range for an important cancer biomarker, carcinoembryonic antigen (CEA), which could be found in patient with colorectal, lung, ovarian, pancreatic, breast and liver cancer.

Another case that will be demonstrated is a novel MXene-based electrochemical microfluidic chip that combining the initial dialysis and subsequent detection of three biomarkers in the whole blood (uric acid, urea, and creatinine) [10]. The three biomarkers were quantified simultaneously in one device, and each component detection has proven to be accurate, reliable and interference-free, capable to meet the clinical and civil demands. In terms of point-of-care test (POCT), the MXene-based device was also considered to be a promising candidate with advantages of cost, stability, adaptability in different/adverse detection environments, miniaturization, automation of tests, etc Zhang *et al* have also developed similar devices for quantifying analytes in blood serum samples. The device could simultaneously detect acetaminophen (ACOP) and isoniazid (INZ). The delaminated MXene suspension was used as signal enhancer by coating a screen-printed electrode [41]. These devices open a valuable window for the clinicians to understand patient health and their responses to the clinical treatment by providing continuous measurements and real-time data of a wide range of chemical/biomolecules in patients. The shortcomings are that researchers need to design specific microfabrication for various applications. This requires a related researching background, and also increased device costs. For each sensor, a comprehensive optimization of the operating conditions will also need to be completed in order to obtain the best sensing performance for target analytes. Future research should focus on developing more common and simple devices.

#### 5. MXene-based DNA sensors with NDA nanostructures

Although most of recent researches focus on immobilizing enzymes or protein molecules on MXene nanosheets to make functional electrodes to sense biological materials, another kind of nano-DNA probing sensor has also received increasing attention [18, 42]. The use of DNA nanostructures (DN) and MXene to develop electrochemical DNA (E-DNA) sensors for ultrasensitive detection of biomolecules is starting to draw more attentions. Generally, E-DNA sensors using DNs as interface probes are superior in sensitivity, selectivity, and repeatability compared to traditional sensors using single-stranded DNA (ssDNA) or

double-stranded DNA (dsDNA) probes. These traditional DNA biosensors are expensive and often require complex modification to synthesize DN [18, 43–45]. MXene-based E-NDA sensor seems to be able to solve these issues. Wang Hui and colleagues [18] worked on TDN-modified MXene and applied them as a new interface probe to detect fumigatoxin, one of the most toxic metabolites produced during the growth of *Aspergillus fumigatus*. In the device, MXene served as a flexible and high-conductive scaffold, which facilitate a large number of DNs on the surface of electrodes. In this way, the involved DNs do not need to be complicatedly modified, which greatly reduces the cost and difficulty of operation. Then the fixed DNs could be used as rigid supports to identify target bio-elements. Combining the advantages of two promising nanomaterials, the sensor can detect glial toxins as low as 5 pM in actual samples, and has superior performance compared to previously developed sensors. The findings of relevant research also has shown that MXene-based DNA sensors can easily secure a large number of DNs to the electrode surface due to the large surface area and functional groups on MXene surface [18, 46]. As a result, the DNs involved do not require much modification, which greatly reduce the cost of measurement and difficulty of operation. However, the sensitivity and accuracy of the method still need to be confirmed and more researches should be conducted in future.

## 6. Cytocompatibility

As we mentioned before, MXene present good conductivity and excellent volumetric capacitance, which render MXene and related materials great potentials for various biosensing applications. Nevertheless, in biomedical field, the cytocompatibility of MXene-derived materials still should be regarded as the most crucial parameter and it should be fully evaluated and discussed. Till now, during thousands of emerging MXene paper, only a few reports have reviewed the *in vitro/vivo* cytocompatibility of MXene-based materials. Key information about cellular uptake behavior of MXene-based materials, the influence of surface modifications, *in-vivo* distribution, accumulation, clearance behavior and long-term toxicity remain unknown.

Jastrzębska *et al* have explored some works on the cytotoxicity of the most typical MXene ( $\text{Ti}_3\text{C}_2$ ) to the cancer cells and normal cells [47]. For the normal cells, MXene present a great cellular compatibility of maintaining over 70% cell viability in the whole range of tested concentrations. Surprisingly but significantly, MXene suspensions caused higher cytotoxic effects to cancer cells than to the normal cells. In addition, cancer cells had a higher ROS production in MXene compared to the normal group, suggesting that the possible mechanism of MXene toxicity is related to ROS production. Other forms of MAX phase ( $\text{Ti}_3\text{AlC}_2$ ,  $\text{Ti}_3\text{SiC}_2$ , and  $\text{Ti}_2\text{AlN}$ ) were also explored and all of them showed a good biocompatibility to pre-osteoblasts [48]. The cells are all actively proliferated on all the substrates and showed the good cell compatibility. However, various of parameters (such as composition, size, surface properties, and surface modification) could affect the biocompatibility of nanomaterials [49]. Correlations of MXene structure/properties with the cytocompatibility is still hard to predict, thus further researches need to be conducted. Therefore, for all the newly developed or modified MXene devices, the modification could potentially modulate the cytotoxicity of the materials. More attention should be paid to systematically assessing and adjusting the toxicity of the materials before all the practically biomedical applications of any new MXene-derived devices. The cell uptake behavior, cytotoxic mechanism, *in-vivo* distribution, and long-term *in vivo* toxicity should be carefully examined.

## 7. Conclusions

In summary, as a new member of 2D materials, MXene-based materials have demonstrated their unique advantages for biomedical sensing applications. The MXene-based materials have many outstanding features, such as large surface area, low cytotoxicity, enriched surface functional groups, and significant electronic, mechanical, and physicochemical properties. We here summarize three types of MXene based biosensor: (i) MXene-based sensors via physical adsorption; (ii) MXene-based sensors anchoring antibodies; (iii) MXene-based DNA sensors with NDA nanostructures, and their applications and challenges. Generally speaking, the non-covalent and physical adsorption interaction is easy to fabricate on the MXene-based materials, but not stable enough in some biomedical applications. Such as it is hard to achieve an accurate drug delivery for drug loading strategies on MXene materials due to the loose adsorption. And DNA MXene sensors are still in the beginning and need much more works to ensure sensitivity and accuracy in different applications. Thus, it is necessary to employ various techniques of surface modification and functionalization to overcome current limits and improve the performance of MXene-based materials. On the other hand, while some progress has been made in surface modification and biomedical applications of

MXene-based materials, there are still a long way to go before some practical medical applications due to the limited information of the emerging 2D materials.

Limited reports of the *in vitro/vivo* cytocompatibility of MXene-based materials impose a potential risk on the biomedical applications of these devices. For now, only a few reports have examined the biocompatibility of MXene-derived biosensors *in vitro/vivo*, not even mention the cellular uptake behavior of MXene-derived materials, the effects of surface modification and long-term toxicity of MXene-based materials. More importantly, the information about *in vivo* distribution, accumulation, clearance behavior and long-term toxicity is lacking. We advise that future studies treat the cytotoxicity of the emerging 2D materials more carefully before the practical biomedical applications can begin.

## 8. Outlook

To give some clues on the future research and address these potential challenges, we suggest, on one hand, to employ more novel and effective the surface modifications on the surface of MXenes to meet the needs of different biomedical applications. A more stable but specific modification techniques is expected to achieve a more stable and accurate detection. On the other hand, microfabrication technique is another very promising tool to solve the current issue. For a functional test in sweat and whole blood, novel wearable or flexible MXene sensors based on sophisticated microfabrication offer new opportunity to achieve a larger scale of real-time measurement. To further improve performance, tailoring MXene electronic conductivity is also required. Alter MXenes' Fermi level could help to realize this goal by influence surface terminations. To achieve that, vacuum annealing, electrical biasing, could be employed to de functionalize materials. Furthermore, an intercalation method could be researched, in future, to understand the transitions between metallic and semiconductor-like transport through inter-flake effects. We also suggest future studies can all include a deeper study of the cytotoxicity of MXenes and its composites in organisms. The ultimate goal will aim at final clinical and civil applications of MXene-based biomedical sensors, and it is important for future studies to focus on the easy, cheaper, and controllable fabrication techniques, and the long-term stability of the internal biological elements.

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