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Infection Management of Virus-Diagnosing Biosensors Based on MXenes: An Overview

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The occurrence of sudden viral outbreaks, including (Covid-19, H1N1 flu, H5N1 flu) has globally challenged the existing medical facilities and raised critical concerns about saving affected lives, especially during pandemics. The detection of viral infections at an early stage using biosensors has been proven to be the most effective, economical, and rapid way to combat their outbreak and severity. However, state-of-the-art biosensors possess bottlenecks of long detection time, delayed stage detection, and sophisticated requirements increasing the cost and complexities of biosensing strategies. Recently, using two-dimensional MXenes as a sensing material for architecting biosensors has been touted as game-changing technology in diagnosing viral diseases. The unique surface chemistries with abundant functional terminals, excellent conductivity, tunable electric and optical attributes and high specific surface area have made MXenes an ideal material for architecting virus-diagnosing biosensors. There are numerous detecting modules in MXene-based virus-detecting biosensors based on the principle of detecting various biomolecules like viruses, enzymes, antibodies, proteins, and nucleic acid. This comprehensive review critically summarizes the state-of-the-art MXene-based virus-detecting biosensors, their limitations, potential solutions, and advanced intelligent prospects with the integration of internet-of-things, artificial intelligence, 5G communications, and cloud computing technologies. It will provide a fundamental structure for future research dedicated to intelligent and point-of-care virus detection biosensors.
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Influenza, HIV, HPV, and SARS are viral infections that pose a grave threat to public health and the global economy.[1,2] Thus, efficient, accurate, and rapid diagnosis can distinguish between life and death during viral infections. The virus is a pathogenic microorganism that can cause various diseases in animals, plants, and humans. They can be transmitted through skin contact, body fluids, airborne particles, contact with faces, and the touching of an infected person. The entire virus particle, virion, consists of nucleic acid (either RNA or DNA) and an outer shell of protein. It cannot reproduce by itself but direct the infected susceptible cell machinery to produce more viruses. Therefore, they usually are hard to detect, and their infections are challenging to treat.[3] The recent viral outbreaks boosted the alarm and raised significant worries as the viruses could rapidly spread and turn into a pandemic. Nowadays, a fast diagnosis of viral disease in the early stages is crucial in restricting the viral disease spread and effective treatment. However, the conventional virus detection techniques such as; plaque assays, ELISA, immunoassay, immunofluorescence, PCR-based testing, microscopy, and hemagglutination assay are costly, labor-intensive, time-consuming and require sample preparation expert technicians. At the same time, they are also highly prone to false results.[4]

In order to eliminate the limitation of the conventional methods and provide a fast and accurate diagnosis, biosensors were introduced as a promising biomedical detection method. Biosensors are rapid, cheap, sensitive, specific, and feasible for high-scale production without sample preparation and expert technicians.[5] Biosensors are analytical devices that use biological elements (e.g., microorganisms, receptors, enzymes, antibodies, nucleic acids) to produce a signal in response to the interaction with the tested element. Furthermore, the transducer in the biosensor structure converts produced signals into measurable parameters.

Bio-nanotechnology and nanomaterials are new emerging approaches that provide great potential for designing, fabricating and improving the performance of biosensing systems.[6,7] Bio-nanotechnology offers the opportunity to design nanoparticles varying in size, physical, chemical, mechanical, and magnetic properties for application in biomedical science and medicine.[8,9] These nanomaterials can be used to fabricate biosensors,[10] tissue culture,[11] vaccine development,[12] pharmaceuticals,[13] drug delivery[14] and cancer therapy.[15] Nowadays, two-dimensional materials, including graphene, transition metal dichalcogenides, non-metallic nanosheets, transition metal dioxides, and transition metal carbides and nitrides known as MXenes and Xenes, have attracted extensive interest because of their size and physicochemical properties.[16] Two-dimensional materials have shown the potential to develop biosensors for detecting viruses with microscopic dimensions and high performance in terms of selectivity and sensitivity.[17] Among various types of two-dimensional materials, MXenes have garnered much interest due to their excellent electrical properties, various elemental compositions, and large specific surface areas.[18] MXene, a conductive two-dimensional nanomaterial with abundant surface chemistry, is an ideal carrier for biomolecules such as virus, enzyme, antibody, protein and nucleic acid in biosensing applications.

While a significant number of reviews have been dedicated to MXenes based biosensors,[19–25] to the best of our knowledge, the implementation of these materials for diagnosing viral diseases has not been comprehensively reviewed and analyzed. In this review, we investigate the advantages of MXene-based biosensors for diagnosing

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important viral diseases highlighted by the World Health Organization (WHO).

Emerging Viral Diseases Pandemics

Pathogens from animal vectors (e.g., birds, bats, ticks, etc.) are responsible for approximately 10 million deaths per year.[26] Severe acute respiratory syndrome (SARS) virus, hantavirus, Nipah virus, and human immunodeficiency virus (HIV) are just a few such examples.[27,28] Nowadays, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak is causing coronavirus disease 2019 (COVID-19) pandemic. According to the WHO report, more than 400 million cases of COVID-19 have been reported in more than 220 countries and territories, resulting in more than 5 million deaths since January 2020. Different approaches were employed to differentiate viral infections for clinical purposes. Such methods can include observing the resulting antibodies produced reacting to the infection, examining the viral nucleic acids, the free viral proteins, intact viral particles, and physical checkups. In addition, numerous approaches can be used to separate such analytes for further research, including polymerase chain reaction (PCR) methods, virus cultivation, enzyme-linked immune sorbent assay (ELISA), western blots, and antibody testing.[29,30] Yet, the conventional methods lack immediacy in the analysis course since they require advanced and costly laboratory instruments that can hardly be mobile (Fig. 1). Furthermore, other issues, such as the prolonged and arduous process, are needed to research the virus.[31,32]

Therefore, authorities employ bio-nanotechnology to develop accurate, rapid, and cheap biosensors to detect viruses involved in infections and viral diseases. Since the virus contains nucleoid acid and protein in its structure, biosensors were developed to target these two. Therefore, biological reactions such as; antibody-antigen reaction, receptor-ligand reaction, DNA/RNA-DNA hybridization can conjugate specific biological molecules with nanomaterials. Real-time detection and understandable data generation require virus-sensitive transduction equipment that selectively detects the virus and transmits the detection signal to electronic signals.[33] MXenes are attracting significant attention towards developing biosensor devices due to their multilayered architecture that provides a high surface area for enzyme loading and electrocatalytic processes. Their chemical structures contain hydroxyl (–OH), carbonyl (C=O) and fluorine (–F) groups, which will provide active sites for biomolecule immobilization and good biocompatibility substantiated by the retained long-term enzyme activity over the MXene surface.[34] However, the ability to accurately and selectively detect small amounts of analyte in multi-component systems is an essential requirement for MXene-based biosensors. In order to improve the performance of MXene-based biosensors, several strategies have been implemented, such as ensuring an abundance of active surface sites, controlling the geometry of MXenes, and using MXene-based composites. On the other hand, biosensors can be classified by the way they transduce signals into optical,[35] electrochemical,[36,37] and piezoelectric[38] devices. The following section investigates the performance of different biosensors based on MXene materials in terms of sensitivity, selectivity, and limit of detection (LOD). Furthermore, the advantages of MXene-based biosensors for diagnosing important viral diseases are discussed.

MXene Synthesis and Characteristics for Sensing

The ability to detect small biomes using biosensors requires accurate and selective monitoring for commercial viability. Two-dimensional materials have been anticipated as promising bioreceptor and electrochemical transducers because of the abundant electron-terminal surface functionalities, which mainly attract positively charged biomolecules. MXenes, a novel two-dimensional material with a graphene-like structure, have been widely used for various applications, including metal-ion batteries, supercapacitors, fuel cells, absorbents, electronic devices, and biosensors[39,40] owing to their high electrochemical activity, metallic conductivity, good stability, excellent mechanical properties, and excellent dispersion in aqueous solution.[41] MXenes have a general formulation of $M_{n+1}X_nT_X$, in which n = 1, 2, or 3, representing three common structures (Fig. 2). M stands for an early transition metal including Ti, Mo, and V, X refers to carbon/nitrogen, whereas T_X represents a variety of surface terminations, such as fluorine (−F), hydroxyl (−OH), and/or oxygen (=O).[42]

MXenes are mostly synthesized by removing specific atomic layers of their precursors, for example, MAX or similar phrases. MAX phases are a large family of layered carbides and nitrides with up to 70 members. Etching is essential in preparing MXenes because the strong metallic bond between elements A and M in the MAX phase makes it challenging to exfoliate mechanically. Since M–X bonds are more chemically stable than M–A bonds, selective etching

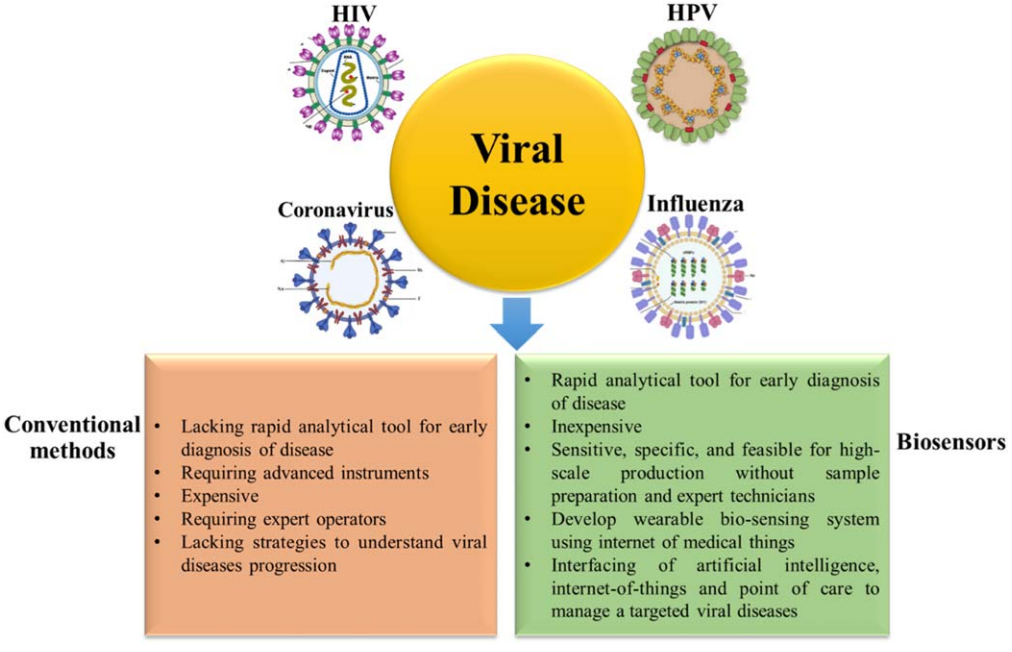

Figure 1. Schematic representation of conventional methods disadvantages and biosensor advantages for diagnosis viral diseases.

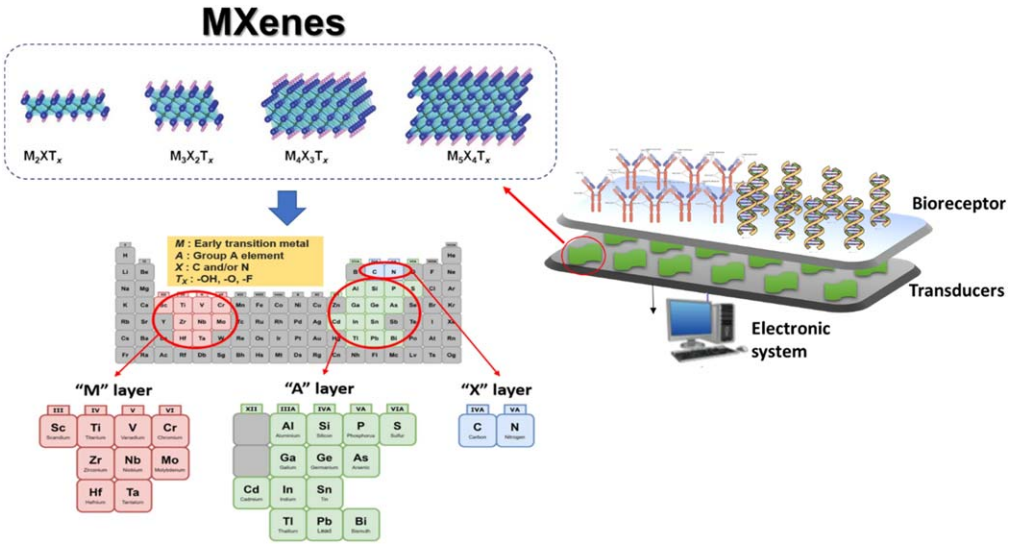

Figure 2. Schematic illustration of MXene-based biosensors.

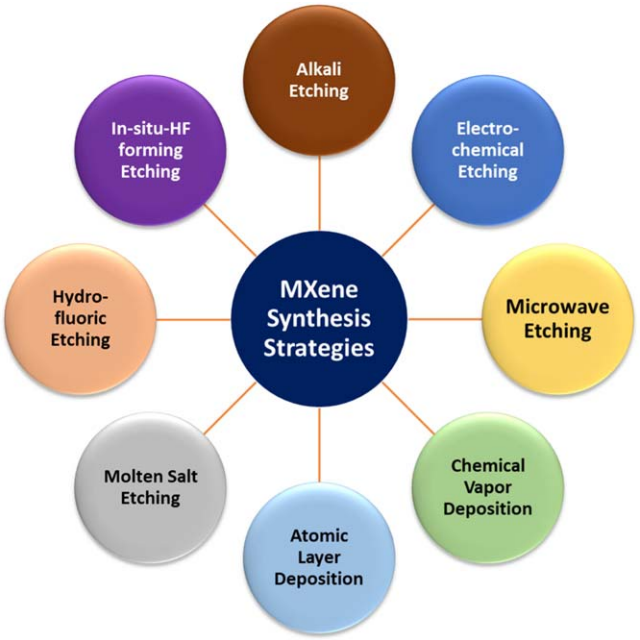

Figure 3. Schematic of MXenes synthesis routes.

of A layers is possible.[43] Typically, MXenes show a compact hexagonal structure. Metalic atoms follow ABABAB sequence in M_2X, whereas M_3X_2 and M_4X_3 follow ABCABC sequence. The MXene sheets are generally aligned laterally, inherited from the parent MAX phases.[44] Among various MXene family members (Titanium Carbide MXene (Ti_2CT_x), Titanium Carbide MXene ($Ti_3C_2T_x$), Tantalum Carbide MXene ($Ta_4C_3T_x$), and Niobium Carbide MXene (Nb_2CT_x)), $Ti_3C_2T_x$ is the most intensively investigated MXene because of the uncomplicated synthesis procedures.[45] Since the discovery of MXenes by Gogotsi team in 2011,[46] MXenes and MXenes-based nanocomposites have been intensively used in sensing or biosensing applications due to their excellent electron transfer capability, good catalytic ability and great biocompatibility.

The most commonly used synthetic methods are top-down and bottom-up synthetic routes (Fig. 3). The etching and delamination procedures can be carried out individually or simultaneously. Wet etching with aqueous hydrofluoric acid (HF) or HF solutions is the main approach for preparing MXenes.[47] The former approach refers to etching "A" element from MAX or non-MAX phases by hydrofluoric acid (HF) solution according to Eqs. 1–3, the most commonly used MXene ($Ti_3C_2T_x$) was synthesized by removing aluminum (Al) from the MAX phase (Ti_3AlC_2) with HF at ambient temperature.[42]

$$2Ti_3AlC_2 + 6HF = 2AlF_3 + 3H_2 + 2Ti_3C_2 \quad [1]$$

$$Ti_3C_2 + 2H_2O = Ti_3C_2(OH)_2 + H_2 \quad [2]$$

$$Ti_3C_2 + 2HF = Ti_3C_2F_2 + H_2 \quad [3]$$

It is reported that the H and F radicals decomposed from HF adsorbed to Ti atoms, weakening Al−Ti bonds, producing surface bonds, and eventually forming $Ti_3C_2T_X$.[48,49] Several MAX phases, such as Ti_2AlC, Ti_3AlCN, Nb_2AlC, Ti_3SiC_2, Mo_2Ga_2C and $Zr_3Al_3C_5$, were successfully transformed into the corresponding MXene nanosheets by using HF as etchant.[50,51] Because chemical etching is a kinetic-controlled process, various important reaction parameters must be considered, including time, temperature, and HF concentration. It was confirmed by Alhabeb and co-workers that effective etching is obtained by a high concentration of HF (30%), forming MXene with accordion morphology, which was not formed during the use of 5% HF.[47]

A molten salt technique (e.g., potassium fluoride, lithium fluoride, and sodium fluoride) was used by Urbankowski and his team for synthesizing Ti_4N_3 based MXene by etching aluminum from Ti_4AlN_3 at 550 °C in Ar.[52]

Mashtalir and his group found that MXene nanosheets could be exfoliated into a single layer by inserting large organic molecules into the interlayers of the accordion-like structure using mechanical vibration or ultrasonication.[53] Tetrabutylammonium hydroxide (TBAOH), dimethyl sulfoxide, hydrazine, urea, and NH_4^+ are commonly utilised as intercalants for MXene exfoliation.[53–55] TBAOH was used as the intercalant by Chia and his team to exfoliate $Ti_3C_2T_X$ MXene from the prepared using HF etching.[56] After removing Al, the micron-sized MAX flakes and the prepared Ti_3C_2-HF were delaminated into single-/fewer-layer MXenes by weakening the interlayer interaction using TBAOH.

In addition, atomic layer deposition and chemical vapor deposition (CVD) as the bottom-up techniques are also used to produce MXene materials. Xu and co-workers deposited α-Mo_2C crystals with size and thickness of 10 μm and 3−20 nm, respectively, on copper utilizing molybdenum foil and methane (CH_4) as the precursors at 1085 °C in hydrogen.[57] Two-dimensional Mo_2C was

formed after molybdenum atoms diffused to the surface of liquid copper and reacted with carbon atoms generated from the decomposition of CH_4. The same method was used for synthesizing TaN and ReC crystals.[42]

MXene materials are highly sensitive and selective detection platforms for biosensing applications because of their outstanding properties, including hydrophilicity, high electrical conductivity, surface area, and attractive topological structure.[58] Unlike graphene, which exhibits excellent conductivity but scarce functional groups, MXene offers abundant hydrophilic terminations for facile electrode modifications and anchoring of biomolecules while retaining attractive conductivity.[59] Besides unique morphology, extraordinary surface chemistry and excellent conducting properties, biocompatibility is among the most prominent features of MXenes, making them a highly suitable matrix for fabricating advanced biosensing platforms. Furthermore, compared to other two-dimensional conductive materials, including graphene, the functional groups endow MXene with more compatibility with other substrates by chemical bond force.[41]

MXene-Based Biosensors

The increasing research interest in applying MXene for fabricating electrochemical sensors is due to good biocompatibility and abundant anchoring sites for loading biorecognition elements, including proteins, enzymes and nucleic acids.[59] The deposition of MXene sensing layer greatly facilitates the anchoring of bi-recognition elements upon electrode interfaces, which is crucial to promote the sensitivity and selectivity of surface-based biosensors.[60] To detect two commonly used drugs Isoniazid (INZ) and acetaminophen (ACOP), $Ti_3C_2T_x$ nanosheets modified screen-printed electrode (SPE) was utilized by Zhang et al.[61] Compared to pristine SPE, the sensor exhibited superior linear detection ranges for ACOP and INZ of 0.25−2000 μM and 0.1−4.6 μM with 0.048 μM and 0.064 μM LODs, respectively (Fig. 4). Furthermore, the obtained $Ti_3C_2T_x$ MXene nanosheets have a negatively charged surface because of the existence of –F, −OH, or =O surface groups, which is beneficial to the aggregation of positively charged analytes.

To detect carbendazim, Wu et al.[62] developed an electrochemical biosensor based on $Ti_3C_2T_x$ with a linear detection range of 50−100 $\times 10^{-6}$ M with a LOD of 10.3 $\times 10^{-9}$ M. The fabricated biosensor exhibited superior selectivity through carbendazim compared to adding ametryn and fenamiphos. Furthermore, Nafion coated $Ti_3C_2T_x$ modified GCE with a range of detection 0.015−10 mM and LOD 3 nM was utilized for dopamine detection by Shahzad and his team.[63] They reported that the performance of the fabricated biosensor was enhanced due to the electrostatic interaction between negatively charged $Ti_3C_2T_x$/Nafion and positively charged dopamine molecules. From the literature, it was reported that the selectivity and sensitivity of biosensors could be improved by using secondary additives in 2D materials. For example, electrochemical biosensors based on MXene/Au/Pt nanoparticles with high selectivity, a linear detection range of 0.4–9.5 $\times 10^{-6}$M and a LOD 0.2 $\times 10^{-6}$ M was developed for the detection of a superoxide molecule produced in the antigen-antibody reaction.[64] The improved sensing performance of the proposed sensor was due to catalytic reactions during the sensing phenomena caused by the addition of secondary components (Au and Pt nanoparticles) to the MXene electrode. The practical viability of using in-vitro analyses of feeding zymosan to Hep-G2 was also investigated. The sensor was reported to detect a minute concentration of the superoxide generated from adding Hep-G2 in 5 μl zymosan. In another study, Mxene/CNT/Prussian blue nanocomposite based electrochemical biosensors were used to detect glucose and lactate.[65] The fabricated sensor was initially modified with lactate oxidase and glucose oxidase enzymes, which generate hydrogen peroxide ionizing the PB in reacting with glucose and lactate. The produced ions react with the MXene-based electrode to induce a redox interaction, increasing electrochemical sensitivity. The developed sensor indicated a linear detection range of 10 $\times 10^{-6}$ M to 1.5 $\times 10^{-3}$ M with 0.33 $\times 10^{-6}$ M LOD for detecting glucose, whilst that of 0 to 22 $\times 10^{-3}$ M with LOD 0.67 $\times 10^{-6}$ M for lactate. To detect lactate, MXene/Pt/PAN nanocomposite based biosensor was reported by Neampet and his group.[66] The fabricated sensor was initially modified utilizing lactate oxidase enzyme and indicated a very low LOD of 5 $\times 10^{-6}$ M. Moreover, surface functionalization and modification have been reported as effective strategies to stabilize 2D materials at the anodic potential window for enhancing biosensing performance. To monitor L-Cys electrochemically, a biosensor based on Pd@ $Ti_3C_2T_x$ hybrid with linear range of detection around 0.5–10 μM and 0.14 μM LOD for L-Cys was fabricated.[67] Furthermore, a $Ti_3C_2T_x$ MXene/graphite nanocomposite based electrochemical biosensor detected adrenaline with 9.5 nM LOD. Moreover, Li et al.[68] reported $Ti_3C_2T_x$ MXene/layered double hydroxides (LDHs) composite for non-enzymatic detection of glucose with a linear detection range 0.002–4.096 mM. The sensing phenomenon was attributed to oxidation of glucose on Ni–Co–LDH in alkaline solution through the reduction of CO (III) to Co (II) and Ni (III) to Ni (II). To immobilize tetrahedral DNA, MXene-$Ti_3C_2T_x$ nanosheets have been used to fabricate a dual function electrochemical biosensor for mycotoxin detection by employing a gliotoxin aptamer with a linear detection range of 5 pM-10 pM with LOD 5 pM.[65] In addition, to monitor creatinine and urea in human body, a dual-function biosensor was developed by immobilizing the urease enzyme on the surface functionality of MXene through glutaraldehyde.[34] It was reported that the fabricated sensor indicated a linear detection range of 0–3 $\times 10^{-3}$M with a LOD around 0.02 $\times 10^{-3}$M for urea, whilst that of 10–400 $\times 10^{-6}$M with a LOD of 1.2 $\times 10^{-6}$M for creatinine.

In Fig. 5a, $Ti_3C_2T_x$ MXene was used to form a composite film with Nafion for the solid-state electrogenerated chemiluminescence (ECL) sensor construction and was reported by Fang et al..[69] They found that using $Ti_3C_2T_x$ not only allows the composite film to have much higher conductivity but also enhances the adsorption amount of $Ru(bpy)_3^{2+}$ on the electrode surface for single-nucleotide mismatch discrimination detection in human urine. Zhang and his group fabricated an ECL biosensor[70] to detect exosomes using aptamer modified two-dimensional material Ti_3C_2 MXenes nanosheets as the ECL nanoprobe because of its large surface area, excellent conductivity and catalytic properties. Exosomes, nanoscale extracellular vesicles with sizes of 30–100 nm, have been reported to play an important role in the anti-tumour immune response, tumour diagnosis and other processes and are promising biomarkers for early cancer diagnosis.[71] Several techniques have been utilized to detect exosomes, such as western blot, flow cytometry, enzyme-linked immunosorbent, colorimetric, Nanoparticle Tracking Analysis (NTA), and tunable pores.[72–76] However, they are still challenging in simplifying analysis procedures, reducing costs, and improving sensitivity for exosome detection. Figure 5b indicates the construction of the ECL biosensor based on MXenes-Apt2 nanoprobe to detect exosomes. To provide more carboxyl for immobilizing Apt1, PNIPAM-AuNPs composite layer was first coated on the GCE surface. The Apt1 can recognize the EpCAM on the surface of exosomes with high affinity. After exosomes were captured, the electrodes were incubated in the solution with MXenes-Apt2 nanoprobe forming a sandwich-type system based on the highly specific recognition between Apt2 and exosomes. MXenes nanosheets serve as a carrier that can load a bulk of Apt2 for trapping exosomes to provide a substantial surface area. MXenes nanosheets are also used to catalyse the ECL process of luminal. Due to the superior electron transfer properties of MXenes nanosheets, it is possible to increase electron transfer at the electrode interface, increasing the sensitivity of the as-designed ECL biosensor for exosome detection. Zhang and his group reported that the prepared ECL based on Ti_3C_2 MXenes nanosheets for exosome detection exhibited higher sensitivity with a lower detection limit of 125 particles μl^{-1} compared to conventional detection techniques.[70]

Carcinoembryonic antigen (CEA) is another cancer biomarker that elevates many malignancies, such as gastric cancer, colorectal cancer, breast cancer, liver cancer, and pancreatic cancer.[77] In

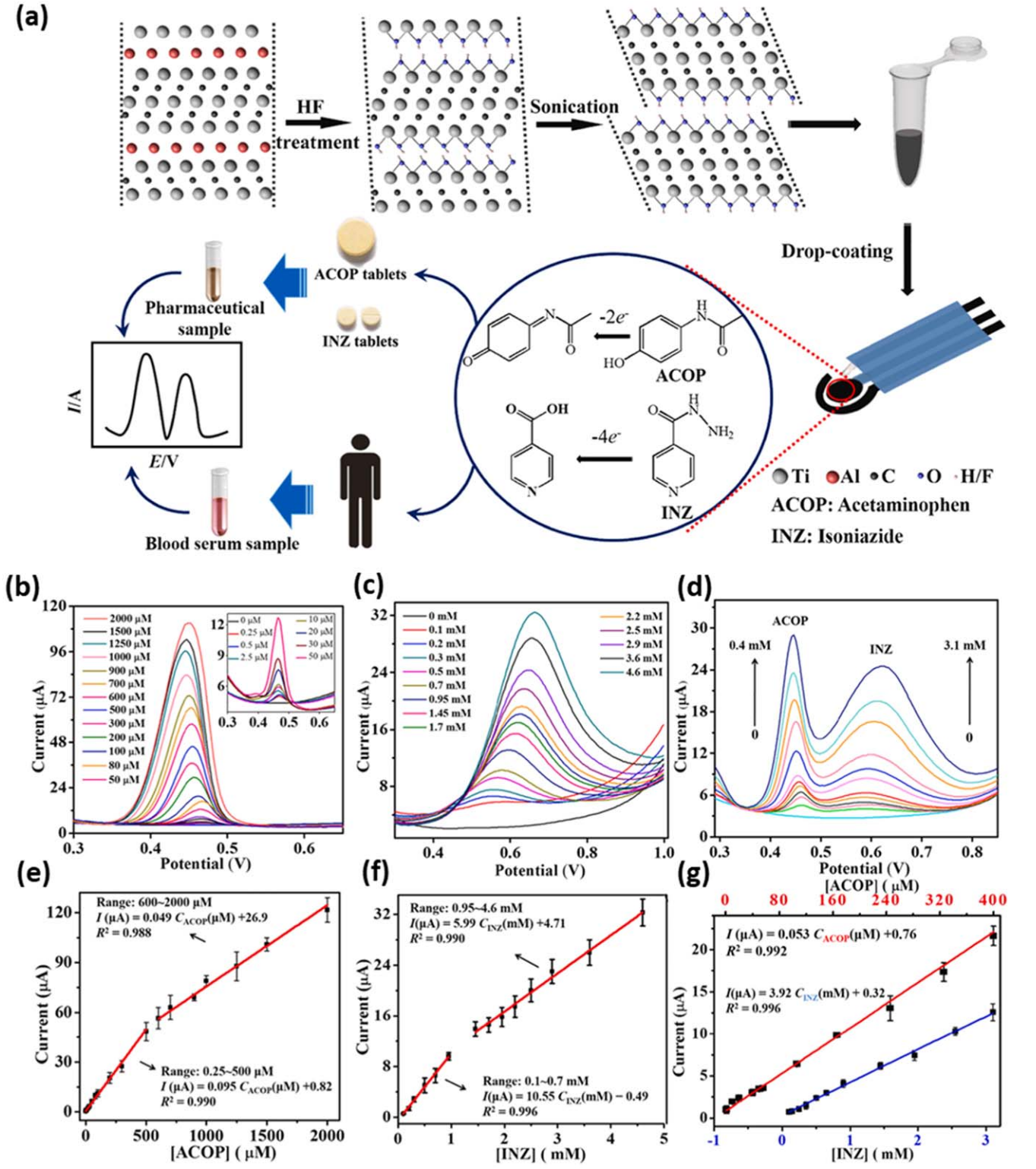

Figure 4. (a) Representation of MXene fabrication and electrocatalytic oxidation process and sensing of INZ and ACOP uilizing SPE/MXene and their Differential pulse voltammograms towards various concentrations of ACOP (b) INZ (d) in 0.1 M H_2SO_4, and observed relation of peak currents with concentrations of ACOP (c) and INZ (e) from three analogous evaluations, (f) Differential pulse voltammogram outcomes of GCE-MXene in 0.1 M H_2SO_4 with various concentrations of INZ and ACOP, (g) Observed relationship of the peak current with the concentration of ACOP (red line) and INZ (blue line) during three analogous evaluations.[61]

healthy people, the normal range of serum CEA is lower than 5.0 ng ml^{-1}, which increases rapidly when normal cells become cancerous.[78] Wu et al. developed a surface Plasmon resonance (SPR) using a Ti_3C_2-MXene-based sensing platform and multi-walled carbon nanotube (MWCNTs)-polydopamine (PDA)-Ag nanoparticle (AgNPs) signal enhancer for ultrasensitive CEA

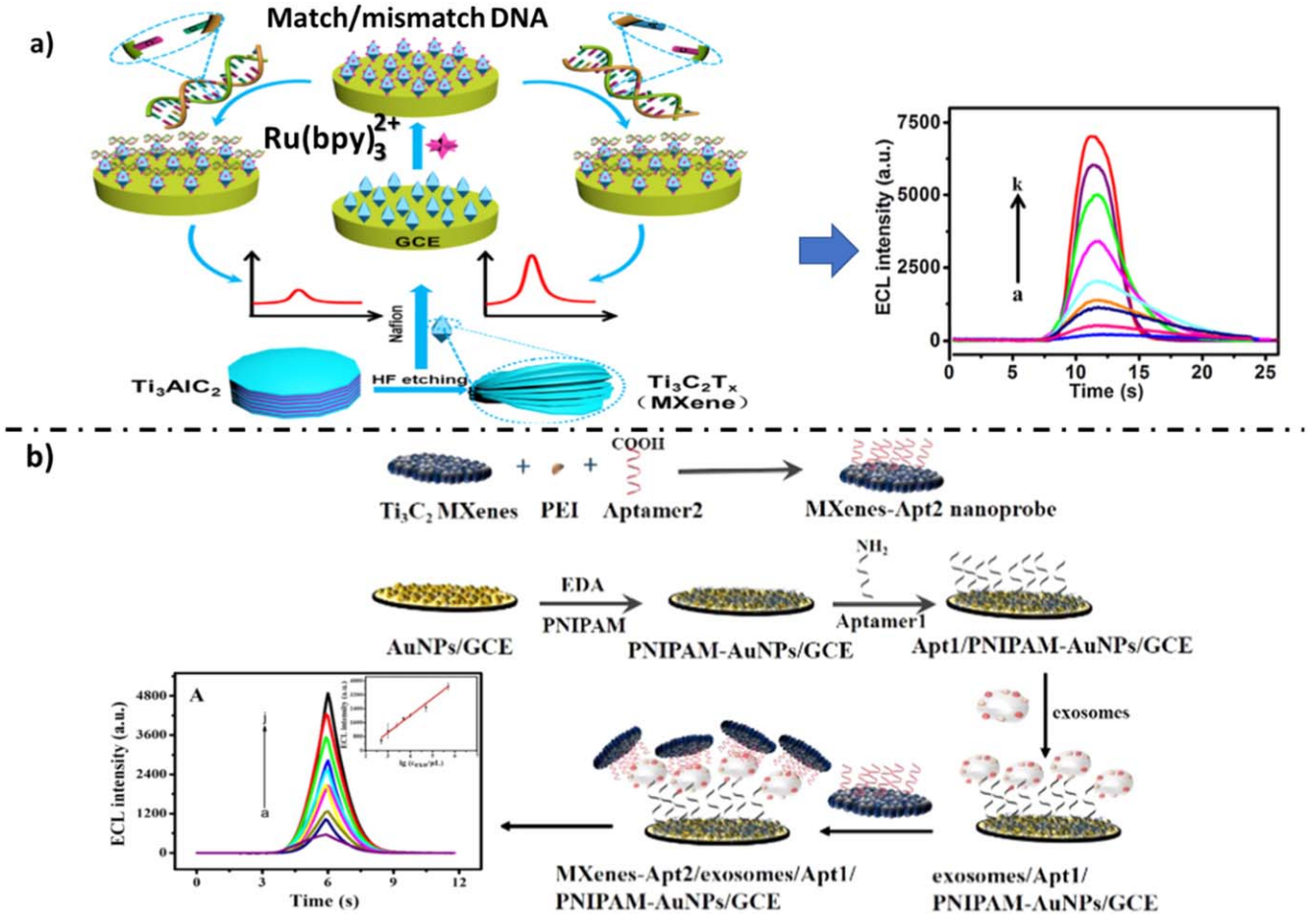

Figure 5. (a) Fabrication of the solid-state ECL sensor based on the GCE,[69] (b) the principle of the ECL biosensor for exosome activity detection signal amplification strategy.[70]

detection.[39] Ti_3C_2-MXene nanosheets suggest a large surface area for loading dense AuNPs-staphylococcal protein A (SPA) without aggregation. In addition, SPA molecules enable oriented immobilization of antibodies, which benefits well for immobilizing more antibodies and protecting their binding sites, enhancing sensitivity. The developed SPR biosensor exhibited an ultralow detection limit of 0.07 fM at a signal-to-noise ratio of 3 s, which is lower than those reported biosensors for CEA detection.[79–82]

MicroRNAs (miRNAs) are one of the main biomarkers for the early diagnosis and prognosis of genetic diseases, including human cancers and neurological diseases.[83] They are a class of about 22 nucleotides, single-stranded non-protein-encoding RNAs, and miRNA-155 is emerging to have a role in the progression of breast cancer.[84] MXene- Ti_3C_2 and Au nanocomposite was utilized to immobilize C-DNA, which was modified with methylene blue (MB) for miRNA-155 detection.[18] There was a large initial electrical signal in the absence of a target, whilst miRNA-155 hybridized to C-DNA, and double-stranded structures were formed in the presence of the target. Upon activating the cleavage reaction with Exo III, C-DNA strands were digested into numerous mononucleotides. The released target DNA could be recycled to hybridize with additional C-DNA, triggering the sequential sequence cleavage reaction. Because of Exo III-assisted target recycling amplification, less C-DNA would be left on the surface of the gold electrode in a specified period. MB was properly used as an electroactive redox indicator and was converted to leucomethylene blue (LB) after a redox reaction. The oxidation peak current difference of MB is proportional to the miRNA-155 concentration, demonstrating that the proposed biosensor has potential applications in miRNA diagnosis.

Table I summarizes the developed biosensors based on MXenes materials. From Table II, it can be concluded that MXene-based biosensors have great potential for diagnosis of various biomarkers due to large specific surface area, excellent biocompatibility, and high electrical conductivity, which enables high loading of biomarkers and fast charge transfer of electrode. The following section discusses the advantages of MXene-based biosensors for diagnosing important viral diseases.

Viral Disease Detection Using MXene-Based Biosensors

Human Immunodeficiency Virus (HIV) Detection.—Human Immunodeficiency Virus (HIV) targets the immune system and weakens people's surveillance and defence systems against infections and some types of cancer, and CD4 cell count typically measures immune function. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which can take 2 to 15 years to develop if not treated, depending on the individual. According to the WHO report published in 2018, since the outbreak of HIV, the fatality number of the infected has grown to 32 million people, with the number of total people infected as 75 million. Therefore, faster identification of the infection and subsequent treatment becomes a challenge in healthcare. While there are self-tests available to be utilized if needed, subsequent tests are still needed to validate the initial results. These tests must be carried out by an authorized health worker in an authorized health centre since the test provided by WHO has the precision required to determine the infection. The antibody reaction to the virus takes up to 28–30 d to be discernible in the meantime, of which the infected is not

Table I. List of developed biosensors based on MXenes.

Type of biosensor	Sensitive layer	Target Biomarker	LOD	References
Electrochemical	$Ti_3C_2T_x$	Acetaminophen	0.048 μM	61
		Isoniazid	0.064 μM	
	$Ti_3C_2T_x$	Carbendazim	10.3 nM	62
	$Ti_3C_2T_x$/Nafion	Dopamine	3.0 nM	63
	Mxene/CNT/Prussian blue modified with lactate	Lactate	0.67 μM	65
	Mxene/CNT/Prussian blue modified with glucose	Glucose	0.33 μM	
	Pd@ $Ti_3C_2T_x$	L-Cys	0.14 μM	67
	Tetrahedral DNA immobilized by $Ti_3C_2T_x$ nanosheets	mycotoxin	5 pM	65
Solid-state electrogenerated chemiluminescence (ECL)	$Ti_3C_2T_x$	exosome	125 μl^{-1}	70
Surface Plasmon resonance	$Ti_3C_2T_x$/ MWCNTs-polydopamine-Ag nanoparticle	Carcinoembryonic antigen (CEA)	0.07 fM	79

Table II. List of developed biosensors based on MXenes for detection of viral diseases.

Viral disease	Type of biosensor	Sensitive layer	Target Biomarker	LOD	References
HIV-1	Electrochemiluminescent	$Ti_3C_2T_x$/ZIF-8	HIV-1 protein	0.3 fM	85
HPV	Fluorescent	MXene Ti_3C_2 nanosheets	HPV-18	10 pM	94
	Piezo-resistive	$Ti_3C_2T_x$-PEDOT:PSS/PDMS	HPV-related DNA	15.22 pM	95
Influenza A (H1N1)	Immobilized Field-effect transistor sensor	Graphene/MXene	Influenza A (H1N1) HA polyclonal antibody	125 copies ml^{-1}	33
Covid-19	Chemo-resistive biosensing	DNA-Functionalized $Ti_3C_2T_x$ MXenes	SARS-CoV-2 Nucleocapsid Gene	10^5 copies ml^{-1}	95
	Surface plasmon resonance	ZnO/MXene	Analytes with reflective index: 1.388–1.422	—	107
		ZnO/Pd/MXene	Analytes with reflective index: 1.388–1.422	—	
	Immobilized Field-effect transistor sensor	Graphene/MXene	SARS-CoV-2 spike antibody	1 fg ml^{-1}	33
	Electrochemiluminescent	PEI-Ru@Ti_3C_2@AuNPs	SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) gene	12.8 aM	108
	Surface plasmon resonance	MXene quantum dots	nucleocapsid of SARS-CoV-2	4.9 pg ml^{-1}	109
	Electrochemiluminescent	Au@Ti_3C_2@PEI-Ru(dcbpy)$_3^{2+}$	SARS-CoV-2 RdRp Gene	0.21 fM	106

detectable. Unfortunately, the "window period" is the main drew back of serological HIV detection test since antibody production against the virus takes a long time and, in some cases, report a false negative result.

Besides, the infected case can potentially transmit the virus in this period. Hence, studies have focused on designing and fabricating nanomaterial-based biosensors to detect infection faster and more accurately. ECL biosensors have recently captured great attention owing to their advantages, including simple instrumentation, quick analysis, high sensitivity, and low cost.[85] Hence, there is still an urgent need to present an advanced material to fabricate a novel ECL biosensor to detect HIV effectively. Recently, Wang and his group fabricated a novel ECL biosensor using a combination of metal-organic frameworks (ZIF-8) with $Ti_3C_2T_x$ as an ECL emitter to detect HIV-1 protein.[85] The SEM images of $Ti_3C_2T_x$ before and after etching by HF are shown in Figs. 6a and 6b, respectively. For the ECL measurement process, $K_2S_2O_4$ was used as a co-reactant, and a negative potential was applied to the electrode so that $S_2O_8^{-2}$ was reduced to the strong oxidants $SO_4^{\cdot-}$ and SO_4^{2-}, and then $SO_4^{\cdot-}$ could also be converted to SO_4^{2-}. After that, $Ti_3C_2T_x$ combined with the electron hole, which was released by $SO_4^{\cdot-}$ to form the excited state species $Ti_3C_2T_x^*$. Finally, the ECL phenomenon could be produced when the excited state $Ti_3C_2T_x^*$ returned to the ground state $Ti_3C_2T_x$.[86,87] Moreover, due to the poor electrical conductivity of $Ti_3C_2T_x$, ZIF-8 was introduced to improve the electrical conductivity of the nanocomposites. To prevent agglomeration between $Ti_3C_2T_x$ layers and provide a platform for ZIF-8 to connect with $Ti_3C_2T_x$, PAA was added to the nanocomposite. The combination of $Ti_3C_2T_x$ and ZIF-8 enabled the co-reactant to disperse rapidly and perform better in terms of ECL. The results demonstrated that the constructed biosensor exhibited excellent sensitivity with a low detection limit of 0.3 fM and remarkable selectivity for HIV-1 protein. The authors utilized $Ti_3C_2T_x$/ZIF-8 nanocomposites to detect HIV-1 in real serum samples and obtained great recoveries ranging from 86.0 to 115.8%, confirming that the prepared biosensor is practical applications and could be used for the detection of HIV-1 in spiked serum samples.

Human Papillomavirus (HPV) Detection.—Nowadays, human papillomavirus (HPV) is estimated to be the most common sexually transmitted infection.[88] HPV prevalence has been found to be highest among young persons within the first few years after sexual debut.[89] HPV is the major human pathogen and the causative agent of cervical cancer. Cervical cancer is the second most common cancer in women, accounting for 527,600 newly diagnosed cases and 265,000 deaths each year worldwide.[90] Conventional analytical methods used for HPV detection include polymerase chain reaction, immunoassays, southern blotting, electrochemical techniques, in situ hybridization, mass spectrometry and microarray.[91–93] A fluorescent biosensor based on MXene Ti_3C_2 nanosheets as a sensing platform was constructed by Peng et al. for selective analysis of HPV.[94] MXene Ti_3C_2 nanosheets prepared by this group illustrated high fluorescence quenching ability to dye-labeled single-stranded DNA (ssDNA) and various affinities for ssDNA and double-stranded DNA (dsDNA). The fabricated fluorescent biosensor for HPV-18 detection exhibited a high specificity with a low detection limit of 100 pM. However, fluorescent biosensors lack effective signal transduction and wireless data transmission technologies, hence limiting their application as smart sensors because it is difficult to balance sensitivity and integrated portability. Zeng et al. have reported the high-sensitivity, wide generality, and portability of the CRISPR-Cas12a-based Ti3C2Tx-PEDOT:PSS/PDMS to overcome these obstacles piezo-resistive biosensor with real-time wireless transmission of the nucleic acid detection signal.[95] They developed a prototype of MXene/PEDOT:PSS-modified flexible interdigitated electrodes with system-level integration of CRISPR-Cas12a-mediated target-activated gas-producing reactions and portable smartphone visual readout to enable real-time and continuous detection of HPV-related DNA (Fig. 6d). Experimental and theoretical simulation results showed that the $Ti_3C_2T_x$-PEDOT:PSS/PDMS

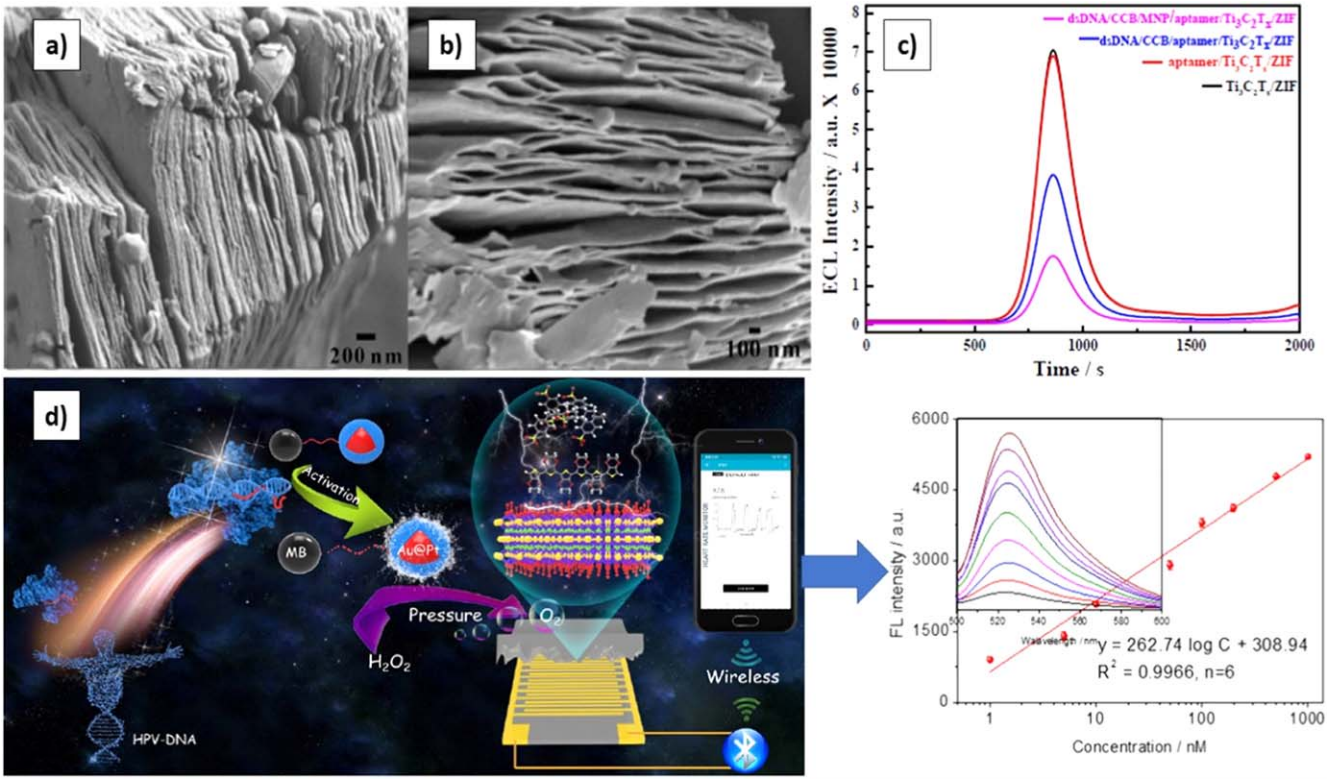

Figure 6. SEM images of (a) $Ti_3C_2T_x$ before etching, (b) $Ti_3C_2T_x$ after etching by HF, (c) ECL signal of different modified electrodes,[85] and (d) schematic illustration of The CRISPR-Cas12a-mediated platform for point-of-care of human papillomavirus (HPV)-related DNA.[95]

with a special microstructure has excellent force-to-electric conversion capabilities. The detection system exhibited good reproducibility and satisfactory accuracy by combining the CRISPR Cas12a-based gas-producing reaction with $Ti_3C_2T_x$-PEDOT:PSS/PDMS wireless biosensor.

Influenza detection.—Influenza is the paradigm of a viral disease in which the continued evolution of the virus is of paramount importance for annual epidemics and occasional pandemics of disease in humans.[96] Influenza is among the many contagious diseases infecting populations with its seasonal spread. Out of all its types, A, B, C, and D, the former is the reason for the seasonal spread of the disease. In addition, type A also includes another group within itself that is categorized based on the residing proteins, namely hemagglutinin (HA) and neuraminidase (NA), on its surface. In the past decade, HA outbreaks have occurred frequently, caused by influenza viruses of subtype H1N1(1918) in Spain, H2N2 (1957) in Asia, H3N2 (1968) in Hong Kong, H5N1 in Asia, Russia, the Middle East, Europe, and Africa (ongoing since 1997); H5N2 in Mexico (1994), Italy (1997), and Texas (2004); H7N1 in Italy (1999); H7N3 in Australia (1994), Pakistan (1994), Chile (2002), and Canada (2003); H7N4 in Australia (1997); and H7N7 in the Netherlands (2003).[97–99]

Among all designed detection methods for influenza infection (RT-PCR, RIDTs, and biosensors), RT-PCR is more accurate and expensive, needs an expert operator, and is time-consuming. Besides, the false-negative result is a typical case in RT-PCR. On the other hand, the RIDTs are fast but inaccurate and cannot be trusted due to false positives. Meanwhile, biosensors have significant detection accuracy, sensitivity, and reasonable price. In addition, biosensors can be designed to target divers' biological biomarkers with great potential in multiple platforms to increase the versatility and accuracy of this virus family. MXene-graphene field-effect transistor (FET) biosensor for influenza virus sensing was developed and characterized by Li and his team.[33] The developed sensor combines the high chemical sensitivity of MXene and the continuity of large-area high-quality graphene to form an ultra-sensitive virus-sensing transduction material (VSTM). Previous studies confirmed the success of using graphene FET sensing for the influenza virus.[100–102] However, due to the relatively low signal-to-noise ratio of the graphene sensing material, the device lacks robustness and requires pre-processing of the virus sample. Therefore, Li and his team[33] decided to develop a 2D MXene-graphene VSTM for FET immune-sensing of influenza. The fabricated sensor based on MXene-graphene composite with a low detection limit (125 copies ml^{-1}) of antigens from inactivated influenza A (H1N1) HA virus exhibited sensitivity of developed biosensor to influenza virus. The average response time was about ∼50 ms, significantly faster than the existing real-time reverse transcription- polymerase chain reaction method (>3 h). The developed FET biosensor was also used to detect 2019-nCoV spike protein ranging from 1 fg ml^{-1} to 10 pg ml^{-1} (Fig. 7a). The sensor demonstrated a linear detection range of 1–10 $pgml^{-1}$ for recombinant 2019-nCoV spike protein with LOD of 1 fg ml^{-1} for recombinant 2019-nCoV spike protein within 50 ms.[31]

Coronavirus detection.—Coronaviruses are a group of related viruses that target the upper respiratory tract of the infected population. The symptoms of the disease can fluctuate between mild or severe infections, whereas with the newer ones, even the danger of fatality has become possible. The most recent coronavirus variant is SARS-CoV-2 resulting in COVID-19 that began spreading worldwide in December 2019, with the source being China. On 11th March 2020, WHO identified the outbreak as a pandemic. More than 400,000,000 cases of SARS-CoV-2 infection have been confirmed globally, and it has claimed more than 5 million lives since Jan 2020. The pathogen responsible for this disease is understood to be a phylogenetic sister to the severe acute respiratory syndrome coronavirus (SARS-CoV), rendering the appointment of the name SARS-CoV-2.[103,104] The real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) method can be used to detect SARS-CoV-2 in oral swabs.[105] Now, results have confirmed the presence of the live virus in stool samples from patients with COVID-19. Like other viral infections, RT-PCR detecting SARS-CoV-2 positive RNA is costly and potentially has false-negative results. In addition, the usual time for having the result is 1–3 d which increases the risk of viral infection distribution. Therefore, biosensors might be a promising solution to all these limitations. To find a fast, efficient, portable, and simple SARS-CoV-2 detection method, Yao, et al.[106] developed a sensitive detection method for the SARS-CoV-2 RdRp gene based on a novel Au@Ti_3C_2@PEI-Ru$(dcbpy)_3^{2+}$ nanocomposite ECL biosensor with an unipedal DNA walker amplification strategy. The ECL biosensor showed sensitivity to the SARS-CoV-2 RdRp gene with a detection range of 1 fM to 100 pM and a limit of detection of 0.21 fM. The potential clinical applicability of the ECL biosensor was further examined by adding various amounts of target DNA to 10-fold diluted human serum, with experimental recoveries ranging from 93.4 to 103.4%. The results confirmed that the ECL biosensor had great application potential for clinical medical detection. Another study proposed two different fiber optic SPR sensor configurations.[107] Both configurations utilize $Ti_3C_2T_x$ as the outermost layer interacting with the analytes. The unique characteristics of $Ti_3C_2T_x$ offer several advantages to finding applications in invasive and non-invasive biosensing of body fluids and VOCs. The Al/ZnO/$Ti_3C_2T_x$ configuration worked effectively for detection analytes with reflective index values of 1.388–1.422 and the Al/ZnO:Pd/$Ti_3C_2T_x$ configuration with 1.354–1.406. They suggested that the proposed biosensor can be an excellent tool for COVID-19 detection as mucus and serum refractive index falls in this range, which is to be explored using real samples.[107] An ECL based PEI-Ru@Ti_3C_2@AuNPs biosensor was developed by Zhang and his team[108] to detect the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) gene. The sensor exhibited a LOD of 12.8 aM for the SARS-CoV-2 RdRp gene. The improved sensitivity is attributed to the role of activated CRISPR-Cas12a, which severs the single-stranded DNA causing the movement of one end of DNA away from the sensor surface. The specificity of the fabricated biosensor is shown in Fig. 7b. Figure 7b indicates that the ECL signal had a greater degree of variation after acting the SARS-CoV-2 RdRp gene (1 fM) on the CRISPR-Cas 12a-based assay system.

Chen and his group recently demonstrated a new facile functionalization strategy for Ti3C2Tx with probe DNA molecules through noncovalent adsorption, eliminating expensive labelling steps and achieving sequence-specific recognition.[95] The Schematic illustration of ssDNA/$Ti_3C_2T_x$ biosensors for SARS-CoV-2 N gene detection is indicated in Fig. 7c. The 2D $Ti_3C_2T_x$ functionalized with complementary DNA probes exhibited a sensitive and selective detection of nucleocapsid (N) gene from SARS-CoV-2 through nucleic acid hybridization and chemo-resistive transduction. Furthermore, the developed biosensor indicated sensitivity through the SARS-CoV-2 (N gene) and fast response, with a detection limit below 10^5 copies ml^{-1} in saliva and high specificity when tested against SARS-CoV-1 and MERS. They also discovered that the interlayer spacing of MXenes may be used as molecular sieve channels for hosting organic molecules and ions, which is a significant benefit in biomolecular sensing.

The biosensors based on MXenes for detecting different viral diseases would shorten the window period and significantly reduce the unwanted virus transmission in this period. This might be an essential step in preventing infection transmission. In addition, these biosensors can be fabricated in high volume to reduce the price. Table II summarizes the developed MXenes-based biosensors for the detection of viral diseases. LOD is one of the important factors for the commercialization of MXene-based biosensors. In general, it can be observed that MXenes is a highly promising alternative sensor material for achieving high sensitivity, exceptionally LOD, and a minimum detectable amount of analytes in biosensing applications.

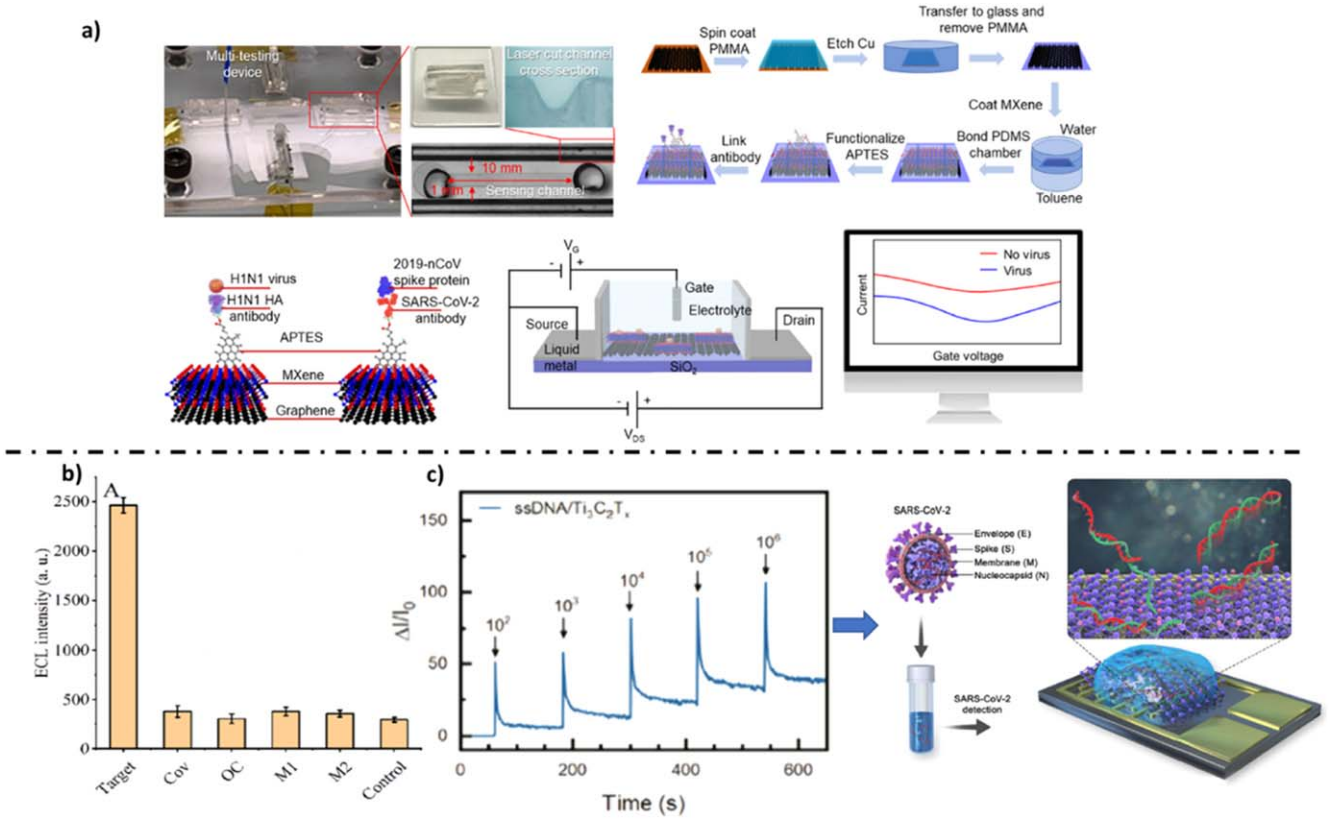

Figure 7. (a) Schematic illustration of MXene-graphene FET sensor for influenza and covid-19 detections,[33] (b) the specificity of ECL based PEI-Ru@Ti_3C_2@AuNPs for different DNA,[108] and (c) Schematic illustration of ssDNA/$Ti_3C_2T_x$ biosensors for SARS-CoV-2 N gene detection.[95]

Challenges and Alternate Solutions

The major challenge associated with the engineering and architecture of MXene-based biosensors is the lack of scalable and sustainable manufacturing of MXenes. Typically, MXenes are synthesized using the HF etchant method, which is neither environmentally nor manufacturer friendly. HF is highly corrosive and volatile in nature, contaminates the environment upon usage, and adversely affects human health upon exposure. The single scalable method reported in the literature for MXene fabrication to date using large-size reactors is also based on the usage of HF as an etchant. However, there have been other studies on using moderate etchants such as LiF, HCl, or their mixtures for manufacturing MXenes, although the generation of in situ HF during synthesis remains a problem in terms of safety and sustainability. Although there are reports on alternative methods for MXene production, including CVD, their use is restricted due to low yield and to a specific class of MXene. Thus, exploring other sustainable, safer, greener and economic strategies is required, such as using green chemistry based on utilizing biomes for manufacturing MXenes. Moreover, the challenge of maintaining electrical conductivity and mechanical endurance simultaneously is evident during machine processability. It can be addressed by introducing secondary nanomaterials during MXene synthesis or fabricating their hybrid nanocomposites. Upon manufacture, the next challenge related to MXene is its stability in oxygen and humid environment and restacking of its layers. Intercalating MXene layers prevent the restacking with various materials such as metal ions, polymers and inorganic phases. The introduction of these secondary materials increases the interlayer distance preventing its restacking. However, optimising the precursors in such a case is crucial to maintain its electrical and optical attributes and increase interlayer distance. Further, the manufactured MXene can be prevented from oxidation or interaction with environmental humidity with appropriate surface treatment or functionalization. The excess usage of MXene-based biosensors can also raise the concern of environmental contamination upon using and producing nano-waste. However, the MXenes on appropriate treatment can be used for various purposes such as energy production, harvesting and storage, which elaborates its sustainable significance. Thus, all the challenges associated with architecting MXene-based biosensors can be tackled by engineering MXene surface and chemistries and requires dedicated attention of the research community.

Future Prospective

The combination of MXenes with unique characteristics and bioreceptors with high specificity and affinity provides promising opportunities for different biosensing applications. However, some variations in synthesis protocols can still be tested to improve the productivity and efficiency of MXenes-based materials for diagnostic applications. MXenes have a lot of potential for use as biosensors due to their appealing electrical, optical, mechanical, magnetic, and thermal properties, but they are still in the early stages of development. In contrast to other conventional sensors, they nevertheless confront several difficulties in both the present and future markets. More research on how lab-to-practical nano-diagnostics is needed. In addition, the size, thickness, surface modification, and quality of MXenes should be tuned based on their properties and application. Furthermore, there is also a need for precise control, reproducible, safe, reliable and standardised manufacturing and characterization techniques.

Despite the advances, there is still an urgent need for proper and precise biosensors in hospitals to prevent these potential health risks. Future developments may make biosensing technologies more accessible for low-cost and point-of-care applications. Future studies should be planned to find and design innovative and next-generation non-invasive, specific, affordable, and fast biosensing methodologies and technologies for diagnostic applications, to manage pandemics and life-threatening infectious diseases in particular.

Moreover, the integration of advanced technologies, including artificial intelligence, machine learning, 5 G communication, data computing, cloud computing, and internet-of-things, can shift the paradigm of point-of-care 5th generation of MXene-based biosensors to point-of-solution or solution-on-chip based biosensors.[25] It will provide remote access to such technologies to every user, irrespective of location. For example, a medical center may be set up with experts, which can be connected to a user adopting MXene-based diagnostic remedies in any remote area in the vicinity of medical facilities or restrictions due to the infectious nature of the causable virus. It will enable self-access to the test results based on pre-trained algorithms. Moreover, the integration of artificial intelligence will help detect the virus by biosensor and take action upon recognizing such virus, which opens prospects for point-of-solution biosensing modules. Integrating all the technologies on a single chip of biosensors can lead to the development of solution-on-chip or hospital-on-chip modules, which is the future of diagnostic technologies.[97] Hence, MXene-based biosensor integrated with advanced technologies is predicted in the near future to raise the new paradigm of intelligent, smart, rapid, economical, selective, and sensitive virus-diagnostic strategies to prevent future public health emergencies.

Conclusions

This review paper focused on diagnosing some important viral diseases using MXene-based biosensors. Bio-nanotechnology is a newly emerging approach that provides great potential for designing, fabricating, and improving the performance of biosensing systems. MXene, a two-dimensional nanomaterial with abundant surface chemistry, is an ideal carrier for biomolecules like viruses, enzymes, antibodies, proteins, and nucleic acid in biosensing applications. MXene-based biosensors have great potential for diagnosis of different biomarkers owing to their large specific surface area, excellent biocompatibility, and high electrical conductivity, which enables high loading of biomarkers and fast charge transfer of electrodes. The synthesized MXene-based materials improve the sensitivity and performance of the biosensors and introduce new transducer signaling methods. Biosensors based on MXenes have the potential to be allies in the early detection of viral diseases by offering novel approaches to achieve sensitive, specific, and stable recognition in complex matrices in quick or real-time diagnostics. MXene-based biosensors can be considered a promising candidate for the early diagnosis of viral diseases with low detection limits, fast response, and cost-efficiency. Despite these encouraging properties, very few examples of biosensors based on MXenes for viral disease detection have been developed and successfully applied in real clinical analysis. Most studies investigated Ti-based MXenes and sensitivity improvement of MXene-based biosensors for viral disease detection. However, MXenes using alternative metals such as Nb, V, and Mo also have unique properties that have attracted much attention as suitable candidates for biosensing applications.

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