Exosomes that carry large amounts of tumor-specific molecular information have been identified as a potential non-invasive biomarker for early warning of cancer. In this work, we reported an enzyme-assisted photoelectrochemical (PEC) biosensor for quantification of exosomes based on the in situ synthesis of Ti$_3$C$_2$ MXene/CdS composites with magnetic separation technology and hybridization chain reaction (HCR). First, exosomes were specifically bound between aptamer-labeled magnetic beads (CD63-MBs) and a cholesterol-labeled DNA anchor. The properly designed anchor ends acted as a trigger to enrich the alkaline phosphatase (ALP) through HCR. It catalyzed more sodium thiophosphate ($\text{S}_2\text{P}^\text{2-}$), which combined with Cd$^{2+}$ for in situ fabrication of CdS on Ti$_3$C$_2$ MXene resulting in elevated photocurrent. The Ti$_3$C$_2$ MXene-anchored PEC method was realized for the quantitative detection of exosomes, which exhibited the dynamic working range from $7.3 \times 10^3$ particles per mL to $3.285 \times 10^6$ particles per mL with a limit of detection of $7.875 \times 10^4$ particles per mL. The strategy showed acceptable stability, high sensitivity, rapid response and excellent selectivity. Furthermore, we believe that the PEC biosensor has huge potential as a routine bioassay method for the precise quantification of exosomes from breast cancer in the future.

**Introduction**

Exosomes are a small homogeneous (50–150 nm) subgroup of membrane vesicles originating from late endosomes and secretions, which carry tumor-specific biomolecules, including lipids, proteins, and nucleic acids.$^{1,2}$ Besides, exosomes are secreted by all types of cells and can be detected in a variety of body fluids, including blood, breast milk, tears, urine, amniotic fluid and saliva.$^{1,4}$ The body fluid samples are easy to obtain, and most body fluids are sampled without causing any damage to the body. Therefore, exosomes are widely recognized as a potential non-invasive biomarker for bioanalytical applications, cancer surveillance and disease therapeutics.$^3$

Currently, increasingly new technologies have been proposed to improve the sensitivity of exosomes, including surface enhanced Raman scattering (SERS),$^4$ electrochemistry,$^7$ plasmonic sensors,$^8$ localized surface plasmon resonance (LSPR),$^9$ colorimetry$^{10}$ and so on. However, some analytical techniques for exosome quantification relies on expensive and specialized instruments with the expertise to operate. Therefore, it is urgent to develop novel, highly sensitive and reliable diagnostic techniques for tumor exosomes detection in the clinical research.

Compared with other methods, the PEC biosensor with higher sensitivity and lower background signal provides an emerging approach,$^{11,12}$ which is based on the photo-generated electron transfer between the solution and the electrode surface under the irradiation of light.$^{13,14}$ Seeking high performance materials is an effective means to break through the bottleneck of PEC biosensor. Two-dimensional nanomaterials, transition metal carbides/carbonitrides (MXenes), have attracted tremendous attention to areas of importance in recent years due to their ultrathin structure and excellent physiochemical properties. As has been reported,$^{15–17}$ MXenes are synthesized by extracting a kind of element A from the layered ternary carbides of MAX phase, where M stand for an early transition metal (V,
Cr, Nb, Mo, Mn, Sc, Ti, Zr, Hf, Ta), A is a member from 12–16 A-group element (S, P, As, Pb, Ti, Cd, In, Sn, Ge, Ga, Si, Al), and X is either C or N. MXene not only has metal-like electrical conductivity, but also has excellent chemical reactivity and hydrophilicity due to its abundant functional groups such as –F and –OH on its surface, which is expected to be an ideal matrix material for the construction of nanocomposite structures. However, due to the exposure of a high proportion of metal atoms on the surface, MXene is easily oxidized and accompanied by the collapse of two-dimensional structure. A great deal of efforts has been made to enhance the interfacial interactions between Ti$_3$C$_2$Tx layers, for example, by incorporating polymers or metal ions into Ti$_3$C$_2$T$_x$ as reinforcement fillers. Li et al. reported an effective ion sieving with Al$^{3+}$-intercalated MXene membranes for seawater desalination. Wu et al. prepared hierarchical MoS$_2$/Ti$_3$C$_2$-MXene@C nanohybrids with excellent performance of Li storage and hydrogen evolution reaction, which efficiently stabilized the structure of Ti$_3$C$_2$-MXene and prevented its spontaneous oxidation.

In this work, we took advantage of an enzyme-assisted amplification strategy by hybridization chain reaction to develop the Ti$_3$C$_2$ MXene-anchored PEC biosensor for the detection of exosomes from breast cancer (Scheme 1). The acquisition of enhanced photocurrent signals was derived from the in situ synthesis of CdS nanoparticles on Ti$_3$C$_2$ MXene-modified electrode through the exosomes-initiated DNA cascades. As shown in Scheme 1, a considerable amount of exosomes was specifically captured by the CD63-MBs. Then, the exosome membrane inserted the cholesterol-labeled DNA probe (C1 and C2) and the base sequence from the 5’ end of C2 probe triggered a hybridization chain reaction. Meanwhile, introduction of streptavidin-labeled ALP interacted with the biotin labeled DNA probe (H1 and H2). The ALP catalyzed the p-nitrophenyl phosphate to sulfideion and inorganic phosphate in the presence of thiglycerol. CdS are generated in situ on Ti$_3$C$_2$ MXenes by 1-thioglycerol as a protective agent. The in situ synthesis of CdS nanoparticles on Ti$_3$C$_2$ MXene could effectively inhibit the oxidation of MXene and improve the structural stability due to its physical barrier and limited effect. Furthermore, the Fermi energy level of the two-dimensional Ti$_3$C$_2$ MXene layer could match the band gap energy of CdS, and it is beneficial to the separation and transmission of photo-carriers. The difference between the valence band of CdS and the Fermi level of Ti$_3$C$_2$ MXene led to the formation of a built-in electric field at the interface, which reduced the recombination of electron–hole pairs and increased the PEC signal. Therefore, the concentration of exosomes was a direct reflection of the photocurrent changes from the in situ growth of Ti$_3$C$_2$ MXene/CdS composites, which could be explored for the sensitive detection of low abundance exosomes in breast cancer.

Results and discussion

Characterization of Ti$_3$C$_2$ MXene/CdS composites
The morphology and microstructures of Ti$_3$C$_2$ MXene, CdS and Ti$_3$C$_2$ MXene/CdS composites were observed by scanning
electron microscopy (SEM, Hitachi, SU8010, Japan). Fig. 1A showed the organ-like structure of Ti$_3$C$_2$ MXene after HF corrosion, and the thickness of each layer was about tens of nanometers. As shown in Fig. 1B, we could see clearly that the CdS was granular with diameter of 80~120 nm. From the image of Ti$_3$C$_2$ MXene/CdS composites (Fig. 1C), CdS nanoparticles were embedded in the clearance between layers of the organ-like structure of Ti$_3$C$_2$ MXene. Moreover, elemental mapping was also performed to further confirm the composition and distribution in Ti$_3$C$_2$ MXene/CdS composites. Ti-, C-, Cd-, S- and O-based mappings of Ti$_3$C$_2$ MXene/CdS composites were presented in Fig. 1D–I, revealing that the CdS was uniformly distributed on the surface of Ti$_3$C$_2$ MXene. SEM images proved that the exosomes-triggered HCR signal amplification could successfully generate CdS in situ on the surface of Ti$_3$C$_2$ MXene.

To investigate the phase structure of Ti$_3$C$_2$ MXene, CdS and Ti$_3$C$_2$ MXene/CdS composites, X-ray diffraction (XRD, Rigaku, Miniflex, Japan) was used to characterize the samples. As shown in Fig. 2A, we obtained the XRD pattern of amorphous pure CdS (curve a) catalyzed by ALP, and the diffraction peaks appearing at 26.94°, 44.26°, and 52.04° were indexed to the (111), (220), and (311). Also, the peaks intensities of pure Ti$_3$C$_2$ (curve b) at 8.70°, 18.24°, 28.12°, and 60.94° corresponded to the (002), (004), (006), (110) crystal plane of Ti$_3$C$_2$ MXene, indicating that the Ti$_3$C$_2$ MXene was successfully fabricated. With the in situ fabrication of CdS nanoparticles on Ti$_3$C$_2$ MXene (curve c), the diffraction peak signals of Ti$_3$C$_2$ MXene declined significantly, while the peaks of CdS enhanced gradually. The diffraction peak of Ti$_3$C$_2$/CdS composites (curve c) existed at both 8.70°, 60.94° and 26.94° matched with Ti$_3$C$_2$ MXene and CdS respectively, and other diffraction peaks of Ti$_3$C$_2$ MXene/CdS composites overlapped with those of CdS and Ti$_3$C$_2$ MXene.

This could be interpreted as the fact that CdS generated in situ on the surface of Ti$_3$C$_2$ MXene. The X-ray photoelectron spectrum (XPS, Thermo Fisher Scientific, Verios G 4UC, USA) was used to further investigate the elements of the Ti$_3$C$_2$ MXene/CdS composites on the electrode surface, and accurately measure the internal electron binding energy and chemical states of an atom. As see from Fig. 2B, the survey spectrum of Ti$_3$C$_2$ MXene/CdS composites consisted of predominant elements, including Ti, C, O, Cd, F and S. In addition, the charge of F element could be attributed to the residual HF in the etching process. Fig. 2C shows that a high-resolution XPS spectrum of Cd 3d 411.92 eV and 405.17 eV belonged to Cd 3d$_{3/2}$ and Cd 3d$_{5/2}$, respectively. For the S 2p XPS spectra (Fig. 2C, inset), the binding energy of S 2p$_{3/2}$ and S 2p$_{1/2}$ located at 162.75 eV and 161.51 eV,
respectively. As shown in Fig. 2D, the two peaks of Ti 2p located at 461.14 eV and 455.01 eV, which were attributed to the Ti–C bond.\textsuperscript{22–24} While the other two peaks at 464.54 eV and 458.85 eV were assigned to the Ti–O bond.\textsuperscript{25} The O 1s peaks at approximately 529.4 eV and 531.8 eV (Fig. 2E) might be derived from the bonds of Ti–O–Ti and O–H, respectively.\textsuperscript{26} Furthermore, C 1s could be divided into four characteristic peaks, which located at 281.29 eV, 284.61 eV, 286.54 eV, and 288.43 eV, corresponding chemical bonds with C–Ti, C–C/C–H, C–O, and C–F (Fig. 2F).\textsuperscript{23} All of the above results further confirmed that CdS formed \textit{in situ} in the interlayer space of Ti\textsubscript{3}C\textsubscript{2} MXene.

\textbf{Feasibility of Ti\textsubscript{3}C\textsubscript{2} MXene-anchored PEC biosensor}

In order to further verify the aptamer had been successfully modified to the surface of MBs, the FT-IR spectrum (Thermo Fisher Scientific, Nicolet iS5, USA) of carboxy-modified magnetic beads (curve a) and CD63-modified MBs (curve b) were measured in Fig. S1A.\textsuperscript{†} The CD63 modified-MBs showed the characteristic peaks of methylene asymmetrical C–H stretching (2974 cm\textsuperscript{-1}), C–O stretching vibration (1653 cm\textsuperscript{-1}), N–H bending vibration (1568 cm\textsuperscript{-1}), –OH bending vibration (1319 cm\textsuperscript{-1}) and C=O stretching (1080 cm\textsuperscript{-1}), which demonstrated that CdS had successfully coated amide bond with MBs.\textsuperscript{27,28} As shown in Fig. S1B,\textsuperscript{†} UV-visible (UV-vis) absorption spectrum (Hitachi, U-3900, Japan) were used to monitor the conjugate of MBs-CD63 aptamer (curve a), there was a distinct peak at 269 nm, while the absorption of MBs (curve b) was absent in this region. Obviously, the absorption at 269 nm could be attributed to the characteristic absorption of the CD63 aptamer.\textsuperscript{29} These results verified that the aptamer was grafted to the MBs.

To investigate the feasibility of the Ti\textsubscript{3}C\textsubscript{2} MXene-anchored PEC biosensor for the detection of exosomes, exosomes were extracted from supernatant of MCF-7 cells. The morphology of exosome samples was observed by transmission electron microscope (TEM, HITACHI, HT7800, Japan). Fig. 3A displayed that typical saucer-like exosome particles and had good structural integrity with an average diameter of about 130 nm, whose size and morphology are consistent with previous reports.\textsuperscript{30} In addition, the concentration of isolated exosomes was analyzed by nanoparticle tracking analysis (NTA) as showed in Fig. S2.\textsuperscript{†} The average particle size was about 127 nm, which was consistent with the typical size of exosomes (50–150 nm) and TEM image. Western blot method was used to analyze the effective exosome-specific surface proteins CD81 and TSG101. As shown in Fig. 3B, the test results of CD81 and TSG101 label proteins from the extracted exosomes were both positive by western blot analysis, indicating that the extracted samples were exosomes from MCF-7 cells. These results together confirmed that exosomes had been successfully extracted from MCF-7 cells, so these isolated exosomes could be used for subsequent validation experiments.

In order to confirm the success of the hybrid chain reaction, polypropylene gel electrophoresis (PAGE) analysis was performed in Fig. 3C. Bands 1–4 clearly referred to the DNA sample of C1, C2, H1 and H2, respectively. Lane 5 (C1 + C2) demonstrated the emergence of a new band (about 80 bp), indicating that a hybrid double strand could be formed by mixing C1 and C2. When the bands H1 and H2 were mixed, only a band with an equal base number of H1 and H2 were found, indicating that the two kind of DNA coexisted stably without hybridization chain reaction (Lane 6). When C1 was incubated with H1 and
In this work, to improve the excellent performance of exosome detection, we optimized several conditions, such as Cd\(^{2+}\) concentration, sodium thiophosphate (TP) concentration, 1-thioglycerol (TG) concentration and enzyme-catalyzed reaction time by HCR strategy in the test solution.

First, the concentration of sodium thiophosphate (TP) was optimized from 1 to 10 mM as the substrate for enzyme catalysis (Fig. 4A). The maximum photocurrent was obtained when the TP concentration reached 8.0 mM, and then decreased with the increase of TP concentration, which might be attributed to the excessive deposition of sodium thiophosphate on the electrode, resulting in inhibition of electron and proton transport. Another key factor affecting photocurrent response was the concentration of 1-thioglycerol (TG). The effects of 1-thioglycerol concentration were investigated to evaluate the optimal response of Ti\(_3\)C\(_2\) MXene-anchored PEC system (Fig. 4B). The photocurrent increased sharply with the increase of TG concentration from 0 to 0.7 M. In the presence of 0.7 M TG solution, the photocurrent response value reached the plateau stage, so this concentration of TG (0.7 M) was selected in the follow-up experiments. TG served as ligands of in situ CdS nanoparticles and significantly improved the redox reaction on the electrode surface.\(^{33}\) Therefore, the concentration of TG and TP was 0.7 M and 8 mM for enzyme-catalyzed reaction, respectively. In addition, the concentration of Cd\(^{2+}\) ions had a significant meaning in the in situ generation of CdS nanoparticles on Ti\(_3\)C\(_2\) MXene-modified photo-electrode. The low abundance of Cd\(^{2+}\) might limit the detection range of this proposed PEC sensing platform, and the high-abundant Cd\(^{2+}\) ions might hinder electron transport. As shown in Fig. 4C, when the concentration of Cd\(^{2+}\) was 0.2 M, the photocurrent reached its maximum value. Therefore, 0.2 M Cd\(^{2+}\) was used in the in situ formation process of CdS nanoparticles.

Finally, the influence of the enzyme-catalyzed reaction time for sodium thiophosphate by HCR on the photocurrent was monitored (Fig. 4D). The photocurrent increased with increasing incubation time and the platform was observed at 90 minutes, demonstrating that the whole reaction time reached
Quantitative analysis of exosomes via PEC biosensor

Taking advantage of the above optimal experimental conditions, we further evaluated the performance of our PEC method for quantitative detection of exosomes at different concentrations. Fig. 5A illustrated that an increase in photocurrent intensity with the increase of the exosome concentration from breast cancer. Furthermore, a plot of the photocurrent response against the concentration of exosomes showed a good linear relationship within the detection range of $7.3 \times 10^5$ particles per mL to $7.3 \times 10^8$ particles per mL (Fig. 5B). The corresponding equation correlation equation was $D = 72.920 + 1.172 \times 10^{-6} \times C_{\text{exosomes}}$ ($R^2 = 0.995$). The limit of detection (LOD) of Ti$_3$C$_2$ MXene-anchored PEC biosensor was calculated as $7.875 \times 10^4$ particles per mL, based on $3\sigma/k$ ($\sigma$ and $k$ represent the standard deviation of the blank sample and the slope of the equation, respectively).

The stability, reproducibility and selectivity of the constructed PEC system

In view of practical application, it was of great significance to test the stability, reproducibility and selectivity of Ti$_3$C$_2$ MXene-anchored PEC biosensor. Our proposed PEC approach for exosome detection mainly relied on the specific recognition between aptamer and exosome. To further investigate the selectivity of this PEC biosensor, we used different types of cancer biomarkers in human serum for PEC sensing analysis, e.g. carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), alpha-fetoprotein (AFP), thrombin-antithrombin complex (TAT). As displayed in Fig. 5C, the photocurrent signal generated by exosomes ($7.3 \times 10^6$ particles per mL) was significantly higher than other interferers. And the photocurrent response of other interferers was similar to the background signal. Furthermore, in the presence of $7.3 \times 10^6$ particles per mL exosomes and interfering substance, the photocurrent values were similar to those in the presence of $7.3 \times 10^6$ particles per mL exosomes alone. The result revealed that the interferences had little effect on the detection of exosomes and provided sufficient possibilities for selective detection of exosomes.

The stability of the as-prepared Ti$_3$C$_2$ MXene/Cd$^{2+}$/FTO photoelectrode was monitored by assaying $1.825 \times 10^8$ particles per mL exosomes standard sample. As shown in Fig. 5D, the photocurrent was basically stable and conformed to high stability through the automatic control of “on-off” light irradiation (10 times). The photocurrent response with 10 cycles was recorded with a relative standard deviation of 2.83%. The interaction between Cd$^{2+}$ and oxygen-containing functional groups on the surface of MXene nanosheets could fix the layer spacing. The in situ synthesis of CdS nanoparticles on Ti$_3$C$_2$ MXene could effectively inhibit the oxidation of MXene and improve the structural stability due to its physical barrier and limited effect.

To investigate the reproducibility of the PEC sensor, the photocurrent values of five independently as-prepared Ti$_3$C$_2$ MXene/Cd$^{2+}$/FTO photo-electrode were measured for monitoring $1.825 \times 10^8$ particles per mL exosomes standard. The data indicated that the relative standard deviation (RSD) was calculated as 4.34% As a proof of principle, the above results preliminarily proved the feasibility of PEC scheme and was expected to realize the practical application of exosomes.

Table 1: Recovery results of the spike-in experiment for exosome quantitation in 5% diluted supernatant of fetal bovine serum by the PEC biosensor

| Sample | Spike concentration (particles per mL) | Detected concentration (particles per mL) | Recovery (%) | RSD (%) |
|--------|----------------------------------------|-------------------------------------------|--------------|---------|
| 1      | $7.3 \times 10^6$                      | $6.941 \times 10^6$                      | 95.08        | 2.05    |
| 2      | $7.3 \times 10^7$                      | $7.679 \times 10^7$                      | 105.19       | 1.69    |
| 3      | $1.752 \times 10^8$                    | $1.696 \times 10^8$                      | 96.80        | 3.85    |
Biological sample testing
To explore the potential application of the proposed Ti$_3$C$_2$ MXene-anchored PEC biosensor, we simulated biological samples by injecting exosomes to 5% diluted supernatant of fetal bovine serum. As shown in Table 1, the photocurrent signal increased significantly with the increase of spiked exosomes concentration. The recoveries of exosomes were 95.08–105.19%, indicating that the accuracy of the proposed PEC biosensor for clinical sample testing was acceptable. These observations further demonstrated that our strategy might be of value for the detection of target exosomes in practical application.

Conclusions
In summary, this work established the Ti$_3$C$_2$ MXene-anchored PEC biosensor based on the in situ synthesis of Ti$_3$C$_2$ MXenes/CdS composites by coupling with an enzyme-assisted amplification strategy for the quantitative detection of exosomes. Above all, magnetic separation technology and HCR strategy not only specifically enriched the target exosomes and simplified the operation, which was conducive to the construction of a universal and easy-to-operate platform, but also an amplification strategy to introduce more enzymes through DNA assembly. Such a strategy focused on enzyme-induced CdS deposition on Ti$_3$C$_2$ MXene to form Ti$_3$C$_2$ MXenes/CdS composites, which produced a built-in electric field in the tight interface between CdS and MXenes, and promoted the separation and migration of photo-generated carriers due to the matching energy level. Whereas, our method still has some shortcomings. But still, the proposed strategy remained some reproducibility. As a consequence, our diagnostic approach could provide a viable option for sensitive detection of exosomes and expand to other clinical applications.

Author contributions
Zhenli Qiu: investigation, design of methodology, supervision, writing – review & editing. Dechun Fan: formal analysis, writing – original draft. Xiang Hang Xue: investigation. Jiayi Zhang: investigation. Jiaolin Xu: investigation. Haixia Lyu: conceptualization, supervision, funding acquisition, writing – review & editing. Yiting Chen: conceptualization, supervision, funding acquisition, writing – review & editing.

Conflicts of interest
There are no conflicts to declare.

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