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REVIEW

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Applications and development trend of biosensors in the detection and diagnosis of gastrointestinal tumors

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Abstract

Gastrointestinal malignancies present a significant menace to the well-being of people across the globe. Consequently, the prompt and precise identification of such tumors is of utmost importance. Biosensor technology emerges as a promising avenue in this regard, possessing considerable potential for the detection and diagnosis of gastrointestinal tumors. This is achieved through the integration of biometric components with physical and chemical transducers, enabling rapid, sensitive, and specific detection capabilities. In the context of colorectal cancer, notable advancements have been made in the detection of nucleic acids, proteins, cells, and exosomes. For instance, the detection threshold for miRNA has been refined to the amole level, while the detection methodologies for diverse protein markers are under continuous improvement. In addition, exosome detection techniques are evolving steadily. Esophageal cancer, on the other hand, exhibits its own characteristic enzyme cascade and immune sensors, among others. Similarly, in the detection of gastric cancer, there are numerous innovative approaches for the identification of miRNA, proteins, and exosomes. Looking ahead, the performance of biosensors in tumor detection is anticipated to enhance further. The combination of multiple markers for joint detection is expected to gain prominence, and the realization of integration and miniaturization holds the potential to drive improvements in the diagnosis and treatment of gastrointestinal tumors, ultimately leading to better patient outcomes and a more effective approach to combating these life-threatening diseases.

Keywords: Colorectal cancer, Esophageal cancer, Gastric cancer, Gastrointestinal tumors, Biosensors

Introduction

Gastrointestinal tumors, including colorectal, esophageal, and gastric cancers [1, 2], are a serious challenge facing the global health field, and their morbidity and mortality account for a significant proportion of all types of cancers. Early and accurate detection and diagnosis can improve the treatment effect and prolonging the survival cycle of patients with gastrointestinal tumors [3]. However, traditional

detection methods such as physical examination, medical history analysis, imaging examination, and tissue biopsy have gradually exposed many shortcomings in clinical practice. High-sensitivity biosensor technology can achieve early screening and early detection of tumor-related diseases under the condition of small lesions or low abundance of biomarkers in the early stage of tumors.

Biosensor technology has shown great application potential in the field of gastrointestinal tumor detection and diagnosis. Biosensors can combine biometric elements, such as nucleic acid aptamers, antibodies, enzymes, etc., with physical and chemical transducers (such as electrochemical electrodes, optical components, piezoelectric materials, etc.), to realize rapid, sensitive and specific determination of target analytes (such as tumor-related biomarkers, tumor cells, etc.). It has many advantages, such as simple operation, fast detection speed, small sample size required, and real-time monitoring of tumor-related information at the molecular level, providing strong support for early detection of tumors, disease monitoring, and evaluation of treatment effects.

For example, in the detection of colorectal cancer, biosensors can be analyzed for a variety of biomarkers, including miRNA, protein markers, and abnormal changes, such as gene methylation [4–6], providing an important basis for early diagnosis. In esophageal cancer, novel enzyme cascade biosensors, immunosensors, and optical probes have been developed to detect biomarkers, such as miRNA-144 and Claudin18.2, which help to enhance the precision of early diagnosis for esophageal cancer [7–9]. Substantial advancements have been achieved in gastric cancer detection. Colorimetric biosensors, fluorescence assays, and electrochemical biosensors have been widely used in the detection of miRNA and exosomes, providing new means for the diagnosis and disease monitoring of gastric cancer [10–12].

The previous reviews [13–16] on CRISPR–Cas systems in cancer diagnosis focused mainly on the application of CRISPR–Cas technology in cancer diagnosis, focus on the application of CRISPR/Cas technology in disease detection and diagnosis, from the perspectives of nano-devices for liquid biopsy, the progress of biosensors and bio detection in molecular diagnosis, the detection of specific tumor markers MUC1 mucin based on CRISPR–Cas12a, and the construction of an in vitro diagnostic platform to detect cancer biomarkers. Explore the application potential and optimization direction of this technology in disease detection. These studies are interrelated and progressive, and together provide multi-dimensional ideas and technical support for the development of CRISPR/Cas technology in the field of disease detection, promoting its development in a more accurate and efficient direction. In contrast, this review focused on the application of biosensor technology in the detection and diagnosis of gastrointestinal tumors. Biosensor technology combines biometric elements with physical and chemical sensors to enable rapid, sensitive, and specific determination of target analytes associated with gastrointestinal tumors. It can detect various biomarkers such as microRNAs, protein markers, and gene methylation changes in colorectal, esophageal, and gastric cancers. This has a different research focus from the CRISPR–Cas-based cancer diagnosis review. The novelty of this review is to comprehensively describe the specific applications, advantages, challenges, and future trends of biosensors in the detection

of gastrointestinal tumors, with the aim of providing a comprehensive reference for the timely diagnosis and precision medicine of these tumors.

In summary, the application of biosensor technology in the detection and diagnosis of gastrointestinal tumors is increasingly widespread, and it is expected to overcome many limitations of traditional detection methods. This review will elaborate on the specific application of biosensors in the detection of gastrointestinal tumors, analyze its advantages and challenges in depth, and look forward to future development trends, aiming to offer a comprehensive reference for the timely diagnosis and precision medicine of gastrointestinal tumors.

Colorectal cancer biosensor research

Detection of nucleic acid and protein biomarkers in colorectal cancer

miRNA detection

miRNAs are abnormally expressed in the early stages of colorectal cancer development, such as miR-21 and miR-92a, which are overexpressed in cancer tissues. By detecting these abnormally expressed miRNAs, potential lesions can be detected when the tumor is still in the early and asymptomatic stage, and early diagnosis can be achieved. Early diagnosis can significantly improve the cure rate and survival rate of patients, and improve the prognosis of patients. In addition, during and after colorectal cancer treatment, the expression level of miRNAs in patients changes dynamically with the change of the disease. Regular detection of miRNAs can monitor the progress of the tumor, the treatment effect, and the risk of recurrence in real time. Colorectal cancer in different patients may have different miRNA expression profiles, and these differences can be used for tumor typing. By analyzing the miRNA expression profile, colorectal cancer can be further subdivided into different subtypes, each subtype may have different biological behavior, treatment response and prognosis. In addition, miRNA detection is an additional diagnostic method for colorectal cancer in addition to colonoscopy.

Recently, several cutting-edge researches have focused on the detection of miRNA in colorectal cancer, with significant results. Among them, the detection method based on the RCT–Cas12a system developed by Cheng et al. [4] have successfully achieved high sensitivity for miRNAs closely related to colorectal cancer, such as miR-21, miR-17, miR-31 and miR-92a. The detection limits are as low as 2.1, 1.6, 3.7 and 1.0 pM, respectively, present an important basis for early diagnosis of colorectal cancer. The ratio fluorescence biosensing strategy proposed by Sun et al. [17], cleverly combined with specific nano-platforms and catalytic hairpin assembly technologies, can accurately detect exosomal miR-92a-3p, with a detection limit of 0.047 pM, effectively improving the sensitivity and accuracy of detection. In addition, the PEC biosensor constructed by Sun et al. [18] based on MoS_2@Ti_3C_2 nanohybridization has shown excellent performance in the determination of exosomal miR-92a-3p, with good stability, providing strong support for the diagnosis of gastrointestinal tumors, such as gastric cancer. The cascade isothermal amplification method established by Chen et al. [19] in conjunction with G-quadruplex molecular beacons, which greatly improves the detection efficiency.

Moreover, Wu et al. [20] proposed a SERS strategy based on 3D layered assembly clusters to perform ultra-sensitive quantitative analysis of miR-21 and miR-31, with detection limits reaching an astonishing 3.46aM and 6.49aM, respectively, providing the

possibility for accurate detection of these two miRNAs, which can help detect potential signs of colorectal cancer in the early stage.

The PEC biosensor based on photosensitive hybridization and enzyme signal amplification strategy developed by Sun et al. [21] focuses on the detection of CRC-associated piRNA-823 with an LOD as low as 0.016 fM, which is a highly sensitive detection method that can more accurately capture the molecular changes associated with colorectal cancer. The ratio fluorescent biosensor constructed by Sun et al. [22] not only has high sensitivity, but also can effectively distinguish CRC patients from healthy individuals, providing a reliable basis for clinical diagnosis. What's more, Sun et al. [23] proposed a metal–organic framework (MOF-525) based proportional fluorescence biosensor, which can detect exosomal miR-92a-3p in the range of 0.1–10 pM, and can accurately detect the level change of this miRNA within a certain concentration range.

In addition, Wang et al. [24] concluded that nanogene sensors using free-standing multi-walled carbon nanotube (MWCNT) electrodes perform well in the measurement of miR-21, with a LOD of 1.2×10^{-18} M and a wide linear range. They perform well in human serum samples, providing an efficient and accurate method for the detection of miR-21. Gundagatti et al. [25] reported that electrochemical biosensor has shown unique advantages in quantifying miRNA-204, with high sensitivity, providing a new way for early detection of colorectal cancer.

Recently, the field of miRNA detection for colorectal cancer has shown a vigorous development trend. Many research teams have shown their talents, such as using innovative strategies, such as RCT–Cas12a system and proportional fluorescent biosensing, to create a series of high-sensitivity and high-precision detection methods, which greatly reduce the detection limit and provide key support for early diagnosis, disease monitoring, and tumor classification. However, current research also has shortcomings. On the one hand, some technologies have strict requirements on the experimental environment and operators, making it difficult to popularize in primary medical institutions. On the other hand, there is a lack of uniform standards among different detection methods, and data comparability is poor, which limits the wide application of results. In the future, efforts need to be made to simplify and standardize technologies.

DNA-related testing

In the process of colorectal cancer research, DNA detection technology continues to innovate and develop, providing key support for accurate diagnosis and effective monitoring of the disease. Zhang et al. [26] used flavin adenine dinucleotide (FAD) to assemble black phosphorus nanosheets (BPNS) to construct a self-signal electrochemical sensing platform for the determination of circulating tumor DNA (ctDNA), demonstrating extremely high sensitivity, enabling accurate detection of ctDNA at very low concentrations, providing the possibility. In addition, Luo et al. [27] proposed an integrated strategy for DNA methylation detection based on nanosensor-assisted target-induced nanoparticle coupling and checkpoint-specific base oxidative damage, which can accurately quantify the target DNA methylation ratio, which is of great importance in the diagnosis and monitoring of colorectal cancer and helps to obtain insight into the mechanism of disease onset and progression (Fig. 1).

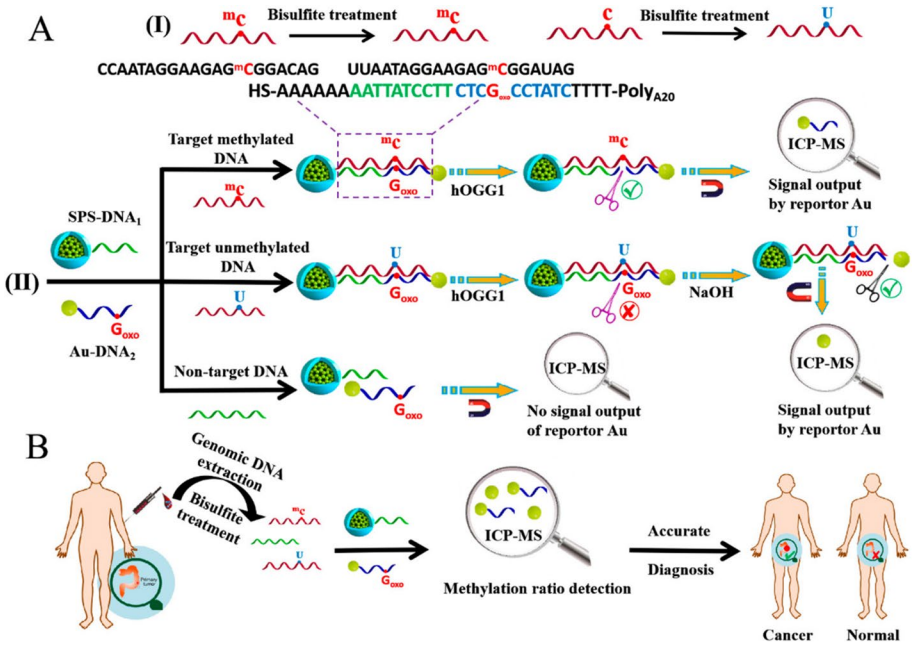

Fig. 1 Depiction of the proposed approach for DNA methylation analysis via target-triggered nanoparticle association and site-selective base oxidation damage reported by Luo et al. [27]

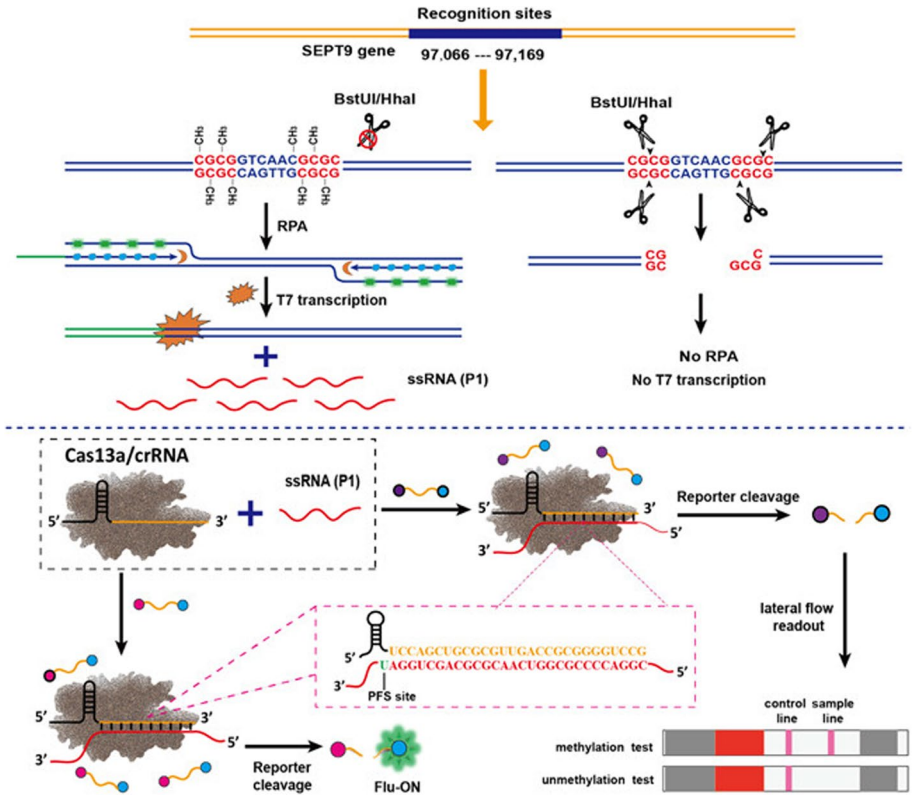

Fig. 2 Schematic illustration shows the DESCS (digestion strategy-assisted CRISPR/Cas13a system) strategy employed in the detection of DNA methylation by Wang et al. [28]

In addition, the digestion strategy-assisted CRISPR/Cas13a system (DESCS) with dual methylation-sensitive restriction enzyme and recombinase polymerase amplification (RPA) developed by Wang et al. [28] (Fig. 2) and integrated into the lateral flow biosensor (LFB) for point-of-care assay of check point-specific DNA methylation can effectively distinguish low methylation levels, providing convenience for rapid detection and diagnosis in the field. Hadian-Ghazvini et al. [29] proposed gene sensors based on polyethyleneimine-stabilized silver nanoparticles (PEI–AgNPs) have a linear response range of 1fM–100 nM when detecting the methylation status of BMP3 genes, and the detection limit of methylation and non-methylation targets is 1fM. These innovative DNA detection technologies analyze DNA molecules related to colorectal cancer from different angles, and play an increasingly important role in improving diagnostic accuracy, monitoring disease progression, and guiding personalized treatment. It is expected to further increase the level of colorectal cancer research and clinical diagnosis and treatment.

The current development of colorectal cancer-related DNA detection technology is rapid, and many teams have innovatively built multi-platform platforms, such as self-signal electrochemical sensing and nano-sensor integration, which have significant advantages, high detection sensitivity and specificity, and can accurately capture key DNA indicators to help diagnosis and treatment; but the shortcomings cannot be ignored. New technologies are often complicated and costly to operate, and the data integration of different methods is difficult, which limits the grassroots promotion and large-scale clinical application (Table 1).

Colorectal cancer protein marker detection

Many protein markers have abnormal expression or secretion changes in the early stage of colorectal cancer, such as carcinoembryonic antigen (CEA), carcinoembryonic antigen (CEA), nucleoside diphosphate kinase NM23-H2 (NDKA), etc. By detecting these protein markers, potential colorectal cancer patients can be identified in asymptomatic populations and achieve early diagnosis. Early diagnosis is crucial to improve the cure rate and survival rate of patients. During the treatment of colorectal cancer patients, the dynamic changes of protein marker levels can reflect the progress of the tumor, the treatment effect and the risk of recurrence. The detection results of protein markers can provide an important basis for the treatment decision of colorectal cancer. Zhang et al. [5] developed a sensor based on molecular imprinted polymers (MIPs) combined with surface-enhanced Raman spectroscopy (SERS) technology for the determination of colorectal cancer markers NDKA. As specific recognition elements, MIPs can accurately capture NDKA, and their imprinting cavity is highly complementary to the target protein with excellent selectivity. Combined with the ultra-sensitivity of SERS technology, the lower detection limit of the sensor is as low as 0.25 pg/mL, which avoids the problem of nanoparticle agglomeration and provides an effective solution for the detection of certain proteins that lack multiple antibody or aptamer binding check points.

In addition, Ma et al. [30] constructed a label-free electrochemical nano-biosensor based on magnetic self-assembly (MSA) technology, with α-Fe–Fe–O/Fe–O nanorods as the core, with its unique magnetic properties to ensure stability, and the aptamer probe self-assembled to form a magnetic probe. When detecting carcinoembryonic antigen (CEA), it showed strong specificity, excellent anti-interference ability and outstanding

Table 1 Detection of nucleic acid and protein biomarkers in colorectal cancer

Detection category	Sensor type	Detection substance	Detection limit	Refs.
miRNA detection	RCT–Cas12a System	miR-21、miR-17、miR-31、miR-92a	2.1, 1.6, 3.7, and 1.0 pM, respectively	[4]
	Ratio fluorescence biosensing strategy	Exosome miR-92a-3p	0.047 pM	[17]
	Nano Hybrid PEC Biosensor Based on MoS_2@Ti_3C_2		0.27fM	[18]
	Cascade isothermal amplification of combined G-quadruplex molecular beacons	miRNA (miRNA-21、miRNA-92a、miRNA-31)	85.8zM, 77.6zM, and 78.9zM, respectively	[19]
	SERS Strategy Based on 3D Hierarchical Assembly Cluster	miR-21, miR-31	The LOD of miR-21 is 3.46aM, and the LOD of miR-31 is 6.49aM	[20]
	PEC biosensor based on photosensitive hybridization and enzyme signal amplification strategy	CRC associated piRNA-823	0.016fM	[21]
	Fluorescence biosensor based on self-assembled fluorescent gold nanoparticles and double-stranded specific nuclease-assisted signal amplification ratio	CRC-associated exosome miR-92a-3p	Can distinguish between patients and healthy individuals	[22]
	Metal Organic Framework (MOF-525) Based Proportional Fluorescence Biosensor	Exosome miR-92a-3p	Detection range is 0.1–10 pM	[23]
	Nanogene Sensors Based on Independent Multi-walled carbon nanotubes (MWCNT) electrodes	miR-21	1.2×10^{-18}m	[24]
	Electrochemical biosensor	miRNA-204	High sensitivity, detection range 15.5aM–15.5 nM, low LOD (suitable for early cancer diagnosis and screening)	[25]
DNA-related testing	Self-Signal Electrochemical Sensing Platform Using Flavin Adenine Dinucleotide (FAD) Assembly of Black Phosphorus Nanosheets	Circulating tumor DNA (ctDNA)	2.6×10^{-19}mol/L	[26]
	Integrated strategy for target-induced nanoparticle-coupling and check point-specific oxidative damage based on carefully designed nanosensors	DNA methylation	Target DNA methylation ratios can be accurately quantified for use in diagnostics and monitoring	[27]
	Coupled digestion strategy based on double methylation-sensitive restriction enzyme and recombinase polymerase amplification (RPA)		can distinguish between low methylation levels	[28]
	Gene sensor based on polyethyleneimine–stabilized silver nanoparticles (PEI–AgNPs)	Methylation status of BMP3 gene	Linear response range 1 fM–100 nM, differential detection limit 1fM	[29]

successful regeneration ability, with a high collection rate of real serum samples, which strongly supported the diagnosis and prognosis of colorectal cancer. Lei et al. [31] prepared a carbon nanotube bridge Ti_3C_2Tx MXene (MX@CNT) electrode array sensor, which can be expanded by template-assisted filtration method, has electrochemical properties The ultra-low background signal and excellent electrocatalytic activity for hydrolyzate were combined with magnetic bead-based alkaline phosphatase ligation immunoassay (MB–aElisa) to achieve high-sensitivity detection of CEA. This method was successfully applied to the detection of serum samples from patients, setting an example for the detection of trace tumor markers. Sun et al. [32] proposed the signal sandwich-like biosensor constructed by L-cysteine–ferrocene–ruthenium nanocomposites (L-Cys–Fc–Ru) uses Ru nanocomponents as signal amplifiers to achieve quantitative detection of CEA based on specific immunorecognition. The detection range is wide (1.0 pg mL^{-1}–100.0 ng mL^{-1}), which has good selectivity, repeatability and stability, and has great potential in clinical applications.

At the same time, other studies have also achieved important results in the detection of protein markers. When detecting CEA, a high-sensitivity metamaterial biosensor based on surface plasmon resonance (SPR) exhibits excellent performance, such as 99.99% perfect absorption at the resonance frequency f (0) = 7.56THz, which can detect clinically significant ng/mL concentrations of CEA [33]. Immunosensors based on graphene oxide (GO) nanocomposites can accurately measure CEA with a linear response range of 0.001–2000 ng/mL [6]. The detection limit of CEA for cancer biomarkers based on THz frequency comb-like detection methods is 0.1 pg/mL [34]. A label-free ultra-sensitive biosensor combining molecular imprinted polymers (MIPs) and SERS technology detects NDKB [35]. The electrochemical immunosensor detects β-1,4-Galactosyltransferase-V (β-1,4-GalT-V), and its linear dynamic range, sensitivity and detection limit are clear [36]. A label-free electrochemical immunosensor based on methylene blue (MB) adsorbed on two-dimensional molybdenum disulfide (2D MoS_2)/graphene oxide (GO) nanocomposites detect matrix metalloproteinase 7 (MMP-7). The relevant detection range and detection limit data also provide reference for clinical detection [37]. These different principles and technologies of protein marker detection methods complement each other and jointly promote the continuous progress of colorectal cancer protein marker detection technology. This is expected to further enhance the accuracy of early colorectal cancer diagnosis and offer more robust support for patients' precise treatment (Table 2).

Detection of colorectal cancer cells and extracellular vesicles

In the field of colorectal cancer research, exosome detection technology is constantly evolving, providing new perspectives and methods for disease diagnosis and research. Chinnappan et al. [38] proposed the "apta-magnetic biosensor" platform, which has the function of isolating, purifying and detecting exosomes from cell culture, provides an effective tool for exosome research and aids in deeply exploring the role of exosomes in colorectal cancer development. The terahertz (THz) metamaterial (MMs) biosensor adopted by Wang et al. [39] focuses on exosome detection and application in the diagnosis of colorectal cancer (CRC). By leveraging the unique advantages of terahertz technology, it offers a new approach for the early diagnosis

Table 2 Colorectal cancer protein marker detection

Detection category	Sensor type	Detection substance	Detection limit	Ref
Colorectal cancer protein marker detection	Sensors based on Molecularly Imprinted Polymers (MIPs) combined with Surface Enhanced Raman Spectroscopy (SERS) technology	NDKB	0.25 pg/mL	[5]
	Label-free electrochemical nanobiosensors using magnetic self-assembly (MSA) technology	CEA	0.197 pg/mL	[30]
	Surface Plasma Resonance (SPR) Based Metamaterial Biosensor with High Sensitivity		S = 1.44THz/RIU, FoM = 26.6RIU^{-1}	[33]
	Graphene Oxide (GO) Nanocomposite Immunosensor		0.001–2000 ng/mL, 0.3 pg/mL	[6]
	Ultrasensitive Detection of Comb Cancer Biomarkers Based on THz Frequency		0.1 pg/mL	[34]
	Electrochemical immunosensor	β-1,4-Galactosyltransferase-V(*β*-1,4-GalT-V)	Linear Dynamic Range 5–150 pM, Sensitivity 14Ω pM, 7 pM	[36]
	Label-free electrochemical immunosensor based on methylene blue (MB) adsorbed on two-dimensional molybdenum disulfide (2D MoS ^{2})/ graphene oxide (GO) nanocomposites	Matrix Metalloproteinase 7 (MMP-7)	Linear logarithm range is 0.010–75 ng mL, 0.007 ng mL	[37]

of CRC and is expected to play a vital role in disease screening. Wang et al. [40] detect exosomes based on a cascade signal amplification strategy based on spherical nucleic acids (SNAs), with extremely high sensitivity, not only can accurately detect exosomes, but also can be used to distinguish between healthy and malignant colorectal cancer patients, providing a reliable basis for clinical diagnosis.

These different exosome detection technologies have promoted the development of colorectal cancer-related research from different aspects. They have their own characteristics in terms of detection limit, detection function and clinical application, and complement each other. With the deepening of research, exosome detection technology is likely to enhance the accuracy of early colorectal cancer diagnosis, help doctors better understand the disease process, and provide strong support for formulating personalized treatment plans, thereby improving the treatment effect and prognosis of colorectal cancer patients. In colorectal cancer research, the detection of circulating extracellular vehicles (EVs) is of great significance. Moreover, Ortega et al. [41] reported that claudin7 (CLD7) in EVs was determined based on microfluidic

amperometric immunosensors. The detection limit reached as low as 0.1 pg/mL^{-1} and the linear range spanned 2–1000 pg/mL^{-1}. This technique can precisely detect the CLD7 content, offering reliable data support for the study of CLD7's role in the development of colorectal cancer. It contributes to a deeper understanding of the pathogenesis of colorectal cancer and provides new technical methods for the early diagnosis and disease monitoring of colorectal cancer.

Other colorectal cancer tests

Gene mutation detection

In colorectal cancer research, gene mutation detection is crucial for accurate disease diagnosis and treatment. The YbTixOy electrolyte–insulator–semiconductor (EIS) biosensor mentioned in Pan et al. [42] perform well in detecting KRAS and BRAF gene mutations in CRC. Its advantages of high sensitivity, low hysteresis voltage, and small drift rate enable it to accurately identify gene mutations, which can be used as an effective diagnostic tool for clinical examination and CRC screening, providing the possibility for early detection and intervention of colorectal cancer. Chowdhury et al. [43] developed an electrochemical biosensor based on differential pulse voltammetry technology that focuses on KRAS mutation detection. It cleverly uses the mismatch-specific cleavage activity of T7-endonuclease I (T7EI) and the catalytic oxidation reaction of horseradish peroxidase (HRP). The detection limit reaches 11.89 μM, and it can distinguish low-proportion mutated genes. This offers a significant foundation for comprehensively understanding the role of KRAS gene mutations in the development and progression of colorectal cancer, and helps doctors develop more targeted treatment plans, playing a key role in the precision medicine of colorectal cancer. These two sensors detect colorectal cancer gene mutations from different angles, jointly promoting the progress of colorectal cancer diagnosis technology.

Comprehensive detection or special detection methods for multiple substances

In colorectal cancer research, a variety of innovative detection technologies continue to emerge, providing more dimensions of support for accurate diagnosis and in-depth research of the disease. The electrochemical biological platform reported by Povedano et al. [44] exhibits a powerful multi-detection capability, capable of detecting 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) in DNA, DNA N6-methyladenine (6 mA) and RNA N6-methyladenosine (m6A). Through the analysis of these molecular markers, it can effectively distinguish the invasiveness of cancer cells, healthy tissues, and tumor tissues of colorectal cancer patients, providing key information for understanding the biological characteristics and pathological process of colorectal cancer.

The novel transverse flow bar assay proposed by Kalligosfyri et al. [45] focuses on the detection of ctDNA mutations in blood samples, especially for colorectal cancer (CRC)-related KRAS gene detection. Its advantages of simple, rapid, and visual detection make it unique in clinical applications. It can be used as an alternative to liquid biopsy applications, providing a convenient means for early screening and diagnosis of colorectal cancer. Moreover, Guo et al. [46] reported that the

Table 3 Detection of colorectal cancer cells and extracellular vesicles and other colorectal cancer tests

Detection category	Sensor type	Detection substance	Detection limit	Refs.
Colorectal cancer exosome detection	"APTA—Magnetic Biosensor" Platform	Exosome	–	[38]
	Terahertz (THz) Metamaterials (MMs) Biosensors		–	[39]
	Signal amplification strategy based on spherical nucleic acids (SNAs) cascade		–	[40]
Detection of specific proteins in circulating extracellular vesicles of colorectal cancer	Microfluidic Ampere Immunosensor	Claudin7 (CLD7) in circulating extracellular vehicles (EVs)	0.1 pg mL^{-1}, 2–1000 pg mL^{-1}	[41]
Colorectal cancer lead ion detection	Tilted Fiber Bragg Grating Surface Plasma Resonance (TFBG–SPR) Biosensor Based on DNAzyme	lead ion	3fM	[47]
Colorectal cancer gene mutation detection	YbTixOy electrolyte–insulator–semiconductor (EIS) Biosensor	KRAS and BRAF gene mutations in CRC	–	[42]
	Electrochemical biosensor based on differential pulse voltammetry	KRAS mutation	11.89 μM	[43]
Comprehensive detection or special detection method for multiple substances in colorectal cancer	Electrochemical biological platform	5-Methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) in DNA, DNA N6-methyladenine (6 mA) and RNA N6-methyladenosine (m6A)	–	[44]
	A new transverse flow bar measurement method	Mutations in ctDNA in blood samples (for CRC-related KRAS gene testing)	–	[45]
	Ag_3PO_4NPs@MoS_2 nanosheet electrochemiluminescence(ECL) Sensing system	K-ras tumor gene	0.2fM	[46]

electrochemiluminescence (ECL) sensing system based on Ag_3PO_4NPs@MoS_2 nanosheets has excellent performance in detecting K-ras tumor genes, which can detect human colorectal cancer tumors and tumor adjacent tissue samples with high sensitivity, offering a powerful tool for the precise detection of tumor genes. These different types of detection technologies work together from the molecular level, the genetic level, and the convenience of clinical detection, help to monitor the progress of the disease, and formulate personalized treatment plans, promoting the continuous development and innovation of colorectal cancer research and clinical diagnosis and treatment technology (Table 3).

Esophageal cancer biosensor research

Enzyme cascade biosensor

In the field of enzyme cascade biosensors, the method reported by Ma et al. [7] for the detection of miRNAs using glucan oxidase (GOX)-mediated oxygen-resistant atom transfer radical polymerization (ATRP) biosensors is an important innovation. This detection method is unique, cost-effective and environmentally friendly, providing the

possibility for the sustainable development of detection technology. At the same time, the sensor has shown excellent performance in the determination of miRNAs, and can accurately detect miRNAs at very low concentrations, which makes it highly promising in early disease determination. For the early stages of a disease, the abnormal expression of miRNA is often an important signal. With its high sensitivity and specificity, this sensor is expected to become a powerful tool for early disease screening, providing a key basis to diagnose and treat subsequent diseases, and promoting the further development of enzyme cascade biosensors in the field of medical detection.

Immunosensor

In the field of biological detection technology, the first immunosensor for detecting Claudin18.2 in Kanagavalli et al. [8] is of great significance. Its innovation lies in immobilizing antibodies by modifying melamine (PM) on different carbon nanomaterials electrodes, to realize the detection of Claudin18.2 protein. This unique design makes the immunosensor have the advantages of high sensitivity and selectivity. Claudin18.2 is abnormally expressed in a variety of cancers. The immunosensor can accurately detect its content, which is of great significance for early cancer diagnosis, disease monitoring and treatment effect evaluation. It is expected to provide strong technical support for clinical diagnosis and treatment of related diseases, and promote research and treatment progress for Claudin18.2-related diseases.

Other sensors

In the field of cancer research, a variety of sensors with diverse functions continue to emerge, providing a wealth of means for cancer detection, monitoring, and research. The surface plasma-tilted fiber Bragg grating (TFBG) biosensor by Qu et al. [48] focuses on the detection of NY-ESO-1 antibodies, which are label-free, compact, and responsive, capable of detecting low concentrations of NY-ESO-1 antibodies. However, there is a hook effect, which provides a direction for subsequent improvement and has certain application potential in the detection of cancer-related antibodies. Li et al. [9] proposed that the new optical probe PEG@ReSe-2 nanosheet plays an important role in monitoring photothermal therapy (PTT) of esophageal cancer cells, with the advantages of high light stability, high biocompatibility and low cytotoxicity, can be used as a visual display of PTT process two-photon probe, help to intuitively understand the photothermal treatment process, optimize the treatment plan.

Li et al. [49] used two-dimensional rhenium disulfide (ReS_2) nanosheets are as novel two-photon luminescence (TPL) probes for intracellular bioimaging, with good photostability and low cytotoxicity. They can effectively monitor photothermal therapy and evaluate treatment outcomes, providing a powerful tool for intracellular imaging and therapeutic effect evaluation. Hsiao et al. [50] used biochips based on silicon solar elements to identify a variety of cancer cells, enabling rapid, label-free measurements through cancer cell dielectrophoresis aggregation and photocurrent response analysis, enabling the differentiation of different types of cancer cells, providing a new approach for early cancer screening and classification. The P-type and N-type PEC biosensors established by Leung et al. [51] detect esophageal cancer cells, and use glutathione-related redox reactions in cancer cells to change photocurrents, which can accurately

identify esophageal cells with different cancer levels, which is helpful for disease monitoring and treatment effect judgment. Tseng et al. [52] reported the highly sensitive PEC biosensor (p-Cu_2O and n-ZnO heterostructures) without external bias for the detection of esophageal cancer cells exhibited high photocurrent gain and low detection limit, allowing for more sensitive detection of cancer cells. Tarimeri et al. [53] proposed ITO-based biosensors detect SOX2. By optimizing electrode modification and incubation conditions, the constructed immunosensors have good analytical performance and can be applied to the detection of real human serum samples, providing a reliable method for the detection of cancer-related markers. These different types of sensors detect and analyze cancer-related indicators from different angles, playing an important role in cancer research, diagnosis and treatment, and promoting the development of cancer precision medicine.

Gastric cancer biosensor research

Gastric cancer miRNA detection

In the field of cancer research, innovative detection technologies continue to emerge, providing key support for the purpose of the prompt detection and precise medical intervention of cancer. For different biomarkers, a variety of detection methods have shown unique advantages. Cai et al. [10] used colorimetric biosensors to detect miRNA-148a using AuNPs combined with RNA probes, with a detection limit of about 1.9 nM, with high sensitivity and selectivity, and AuNP network materials can also provide guidance for biosensor reusability, which is groundbreaking in the development of biomarker detection technology.

A novel approach for the detection of gastric cancer exosomes has been put forward by Huang et al. [11], which is based on the aptamer and branching rolling loop amplification (BRCA) fluorescence assay. Its remarkable specificity holds great potential for the early diagnosis of gastric cancer, thus opening new avenues for the early screening of this malignancy. Liu et al. [12] introduced electrochemical biosensors. These biosensors utilized the localized DNA cascade replacement reaction (L-DCDR) along with universal DNA nanosheets (DNSs). They were capable of detecting exo-miR-21 with a detection limit as low as 65 aM and exhibited favorable specificity. This enabled the successful detection of exo-miR-21 in gastric cancer cell lines as well as in patients. Consequently, it offered a more precise means for the detection of miRNAs associated with gastric cancer.

High sensitivity detection technology is widely used in cancer biomarker detection. With the development of technology, high sensitivity detection technology has been widely used in cancer biomarker detection, which greatly improves the detection accuracy and the ability to detect diseases early. Amoshahi et al. [54] reported an ultrasensitive electrochemical biosensor based on double-stranded specific nuclease-assisted target cycle-binding enzyme signal amplification and Fe_3O_4 nanoparticles detects miRNA-106a with a detection limit of 0.8fM, with high specificity and selectivity, which can more accurately detect trace miRNA-106a. Pan et al. [55] proposed the fluorescent biosensor based on graphite carbon nitride nanosheets (CNNS) detects gastric cancer-related ctDNA in human blood. The detection is realized by the interaction between the unique fluorescein-labeled single-stranded DNA detection probe and the target DNA.

It has the advantages of convenience, low cost and high efficiency, providing a new way for ctDNA detection. Radfar et al. [56] proposed the biosensor based on the signal amplification probe of blackberry-like magnetic DNA/FMMA nanospheres detects miRNA-106a, which performs well in real sample analysis and has potential for early diagnosis and clinical monitoring of gastric cancer, providing a reliable basis for clinical application.

The unique contribution and clinical potential of new biosensors in cancer detection. Many new biosensors continue to show unique performance in cancer detection and have broad prospects in clinical applications. Xia et al. [57] proposed a dual-signal amplification biosensor to detect exosomal miRNA-21, which is superior to serum carcinoembryonic antigen in distinguishing gastric cancer patients from patients with precancerous lesions. The accuracy rate is higher, providing a more accurate judgment basis for gastric cancer diagnosis. In the research by Li et al. [58], it was indicated that an electrochemiluminescence (ECL) biosensor, which was constructed with bimetallic MXene derivative quantum dots (Mo_2TiC_2 QDs) and SnS_2 nanosheets/lipid bilayers, was capable of detecting miRNA-27a-3p, which has potential in clinical application and is expected to become a powerful tool for clinical detection. In the study by Li et al. [59], a biosensor was developed, which was based on bismuth nanonests and Ti_3CN quantum dots and utilized the principle of surface plasmon-coupled electrochemiluminescence (SPC–ECL). This biosensor was designed with the aim of detecting miRNA-421, which has been successfully used in the detection of ascites samples from gastric cancer patients (Fig. 3). It has clinical analysis potential and provides an effective method for the detection of ascites samples from gastric cancer. Chang et al. [60] proposed an ultra-sensitive biosensor based on defect engineering designed in GeP two-dimensional layered materials to detect miR378c with a detection limit of 28.6 aM, which can achieve accurate stage-specific monitoring and contribute to in-depth understanding of disease progression (Fig. 4).

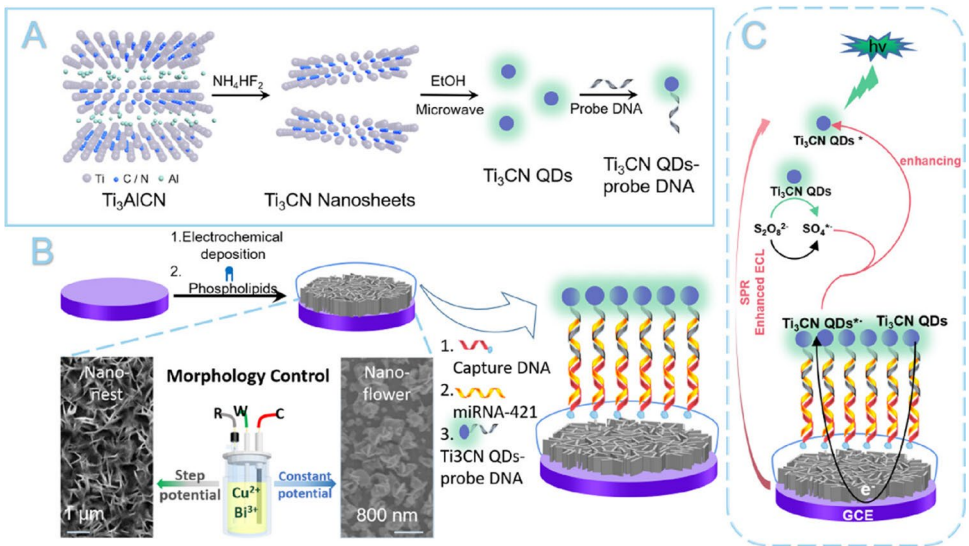

Fig. 3 Illustration of the ECL sensing system founded on Ti3CN QDs and bismuth NN reported by Li et al. [59]

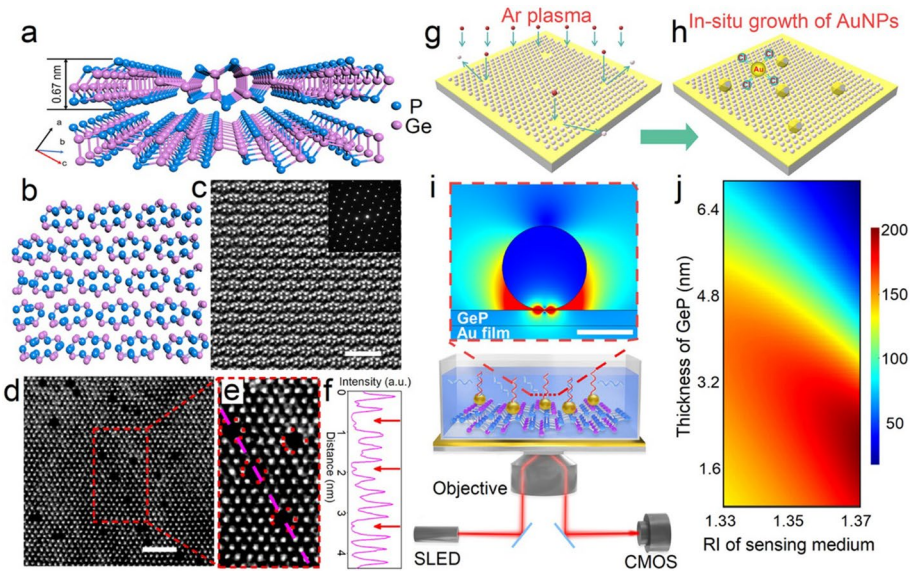

Fig. 4 Crystal structure, single—atom defect engineering, in-situ AuNP functionalization, and plasmonic biosensor of GeP van der Waals crystal reported by Chang et al. [60]

In the field of biosensor technology for cancer diagnosis, El Aamri et al. [61] developed a fluorescent biosensor. This biosensor utilized target catalytic hairpin assembly (CHA) along with enzyme signal amplification. It was designed to detect piR-651, achieving a remarkably low detection limit of 0.1 fM. Moreover, it demonstrated the ability to accurately distinguish piR-651 from other piRs, thus holding great promise for early cancer diagnosis and presenting a novel technical approach in this regard. Meanwhile, Zhu et al. [62] proposed an electrochemical sensor. This sensor was based on the turbo-like localized catalytic hairpin assembly (TL-CHA) mechanism. It was specifically developed to detect sEV-miR1246, attaining an extremely low detection limit of 5.24 aM. The sensor exhibited outstanding performance in the staging diagnosis and early screening of gastric cancer, thereby providing crucial support for the precise diagnosis and effective treatment of this disease. These new biosensors have promoted the progress of cancer detection technology from different angles, bringing new hope to cancer research and clinical practice.

Gastric cancer protein and other markers

In the research and diagnosis of gastric diseases, a variety of marker detection technologies continue to make new breakthroughs, providing important support for the accurate diagnosis and treatment of diseases. For Helicobacter pylori (*H. pylori*)-related markers, Jain et al. [63] proposed a label-free electrochemical immunosensor based on TiO_2 nanoparticles, carboxylated multi-walled carbon nanotubes and conductive polymer composites to detect *H. pylori's* CagA toxin. It has high stability and reproducibility, providing a reliable basis for the diagnosis of Helicobacter pylori infection-related diseases. Xiao et al. [64] proposed a biosensor based on heterologous expression of Helicobacter pylori urease b subunit and nanomaterial modified electrodes for screening Helicobacter pylori urease inhibitors, which not only helps to deeply

understand the pathogenic mechanism of Helicobacter pylori, but also provides a theoretical basis for the development of new drugs. Saxena et al. [65] proposed a MIP-based electrochemical sensing platform for the detection of Helicobacter pylori VacA toxin, with high sensitivity, further improving the detection method of Helicobacter pylori toxin. Saxena et al. [66] proposed an electrochemical immunosensor based on the zeolite imidazolyl ester framework-67 (ZIF-67) derived $Co/Co_3O_4/C$ (CoNH) porous nanostructure to detect Helicobacter pylori specific antigen VacA with high sensitivity and selectivity. It can be used for the early diagnosis of Helicobacter pylori infection and gastric cancer, providing a powerful tool for the early screening of Helicobacter pylori-related gastric cancer.

In addition to Helicobacter pylori-related markers, detection technologies for other gastric disease-related markers are also evolving. Kanagavalli et al. [67] proposed a label-free biosensing strategy based on redox-active melamine electrodeposition on the surface of reduced graphene oxide screen-printed electrodes (PM-rGO/SPE) to detect pepsinogen I (PG I), It has the potential to serve as a diagnostic instrument at the point of care for gastric cancer, providing a convenient on-site detection method for early diagnosis of gastric cancer. Kuche-Meshki et al. [68] proposed a Zn-BTC MOF-based gene sensor self-assembled on a glassy carbon electrode to detect miR-106b, which can be used to evaluate miR-106b in human serum samples, which is helpful for understanding the occurrence and development of gastric diseases at the genetic level. Li et al. [69] proposed a U-cone hollow-core optical fiber (HCF) coated with PtS_3 based surface plasmon resonance (SPR) biosensor for the detection of interleukin-10 (IL-10) and interleukin-1β (IL-1β). This biosensor exhibits high sensitivity and holds the potential to be applied in the early diagnosis of gastric cancer, providing a new way for the detection of early inflammation-related markers in gastric cancer. Liu et al. [70] proposed the detection of carcinoembryonic antigen (CEA) based on a label-free fluorescent biosensing platform combined with aptamer-modified gold nanoparticle (Apt@AuNP) probes and hybridization chain reaction (HRC) amplification, with a detection limit of 0.03 nM, with high selectivity, can be used for clinical sample detection, providing new technical support for the auxiliary diagnosis of gastric cancer and other cancers.

In addition, there are also some detection technologies for other related markers or with special functions that have also shown important value. Shi et al. [71] proposed a sensitive loop-based DNAzyme biosensor (SPOT) for the detection of serum miRNA and SARS-CoV-2 RNA in clinical swabs, showing high sensitivity and specificity. It can be used as a robust method for molecular diagnosis, which is of great significance in the field of viral detection, and provides a reference for the diagnosis of gastric diseases and infections. Wang et al. [72] put forward an AND logic gate-based dual-locking hairpin-mediated catalytic hairpin assembly (DL-CHA), which was utilized for the detection of microRNA and APEl, which can be used as a new method for cancer diagnosis and has important potential applications. It provides a new idea for the innovative development of cancer diagnostic technology. Rohilla et al. [73] proposed a holographic cobalamin (holoTC) based impedance measurement immunosensor to detect holoTC, a vitamin B12 deficiency-related marker, with high selectivity and stability. This represents the initial electrochemical immunosensor designed for holoTC detection, thereby

presenting a novel approach to the detection of nutrition-associated markers. in patients with gastric diseases. These different types of detection technologies have promoted the development of gastric disease-related research and diagnostic technologies in many aspects, laying a solid foundation for improving the diagnosis and treatment of gastric diseases.

Detection of gastric cancerous cells and the associated exosomes

In the field of cancer research, the continuous innovation of detection technology for cancer cells and related biomarkers provides important support for the diagnosis and treatment of cancer. Duan et al. [74] proposed a cell sensor based on Cr-based organic frameworks and cobaltophenocyanine nanoparticles focused on the detection of colorectal cancer (CT26) cells, which has a low detection limit for CT26 cells, and the sensing performance is adjustable, possessing remarkable selectivity and stability along with satisfactory reproducibility, it serves as a potent means for the early detection and continuous monitoring of colorectal cancer. Bai et al. [75] proposed a self-powered biosensor based on photofuel cells for the detection of human epidermal growth factor receptor 2 (HER2), which achieved ultra-sensitive detection by cleverly using plasmon gold nanoparticles and electrochemical sandwich structures. It can be used for the detection of cell lysate samples, which is of great value in the study of HER2-related cancers. Zhang et al. [76] proposed the ultra-sensitive detection of cancer cells based on tapered optical fiber (TOF) biosensors, using the dispersion turning point (DTP) in TOF to effectively improve the sensing sensitivity, with low detection limit for cancer cells, high sensitivity and good selectivity. This shows potential application prospects in the field of chemical and biological detection, providing a new technical means for the accurate detection of cancer cells.

Possessing remarkable selectivity and stability along with satisfactory reproducibility, it serves as a potent means for the early detection and continuous monitoring of colorectal cancer. Fu et al. [77] proposed the detection of gastric cancer exosomes based on magnetron photothermal, colorimetric and fluorescent three-mode aptasensor, and realized multi-modal detection with the help of specific nanocomposite materials and aptamer markers, which can effectively distinguish gastric cancer patients from healthy individuals, providing a new idea for the early diagnosis of gastric cancer (Fig. 5). Zhang et al. [78] proposed the simultaneous detection of gastric cancer biomarkers miR-5585-5p and PLS3mRNA based on dual-target synergistic response fluorescent nanomachines (Fig. 6). The RNA-free, PCR-free and non-enzyme biosensors can achieve tumor cell imaging and serodiagnosis, and the detection limit reaches the fM level. It holds remarkable importance in the diagnosis of gastric cancer, furnishing a more thorough foundation for the precise diagnosis and treatment of this disease. Ma et al. [79] proposed an ECL biosensor based on Cu nanoclusters (Cu NC) grown in situ on metal–organic framework (MOFs) nanosheets to detect miRNA-421 in gastric cancer extracellular vehicles (EVs), which is utilizable for diagnosing the peritoneal metastasis of gastric cancer, providing an important detection method for gastric cancer metastasis-related research. Zhang et al. [80] proposed that biosensors based on quantum dot/hydrogel-coated dual fiber optic spheres (DOFB) sensing structures can identify and detect biotin receptor (BR) overexpression cancer cells, with high sensitivity, specificity

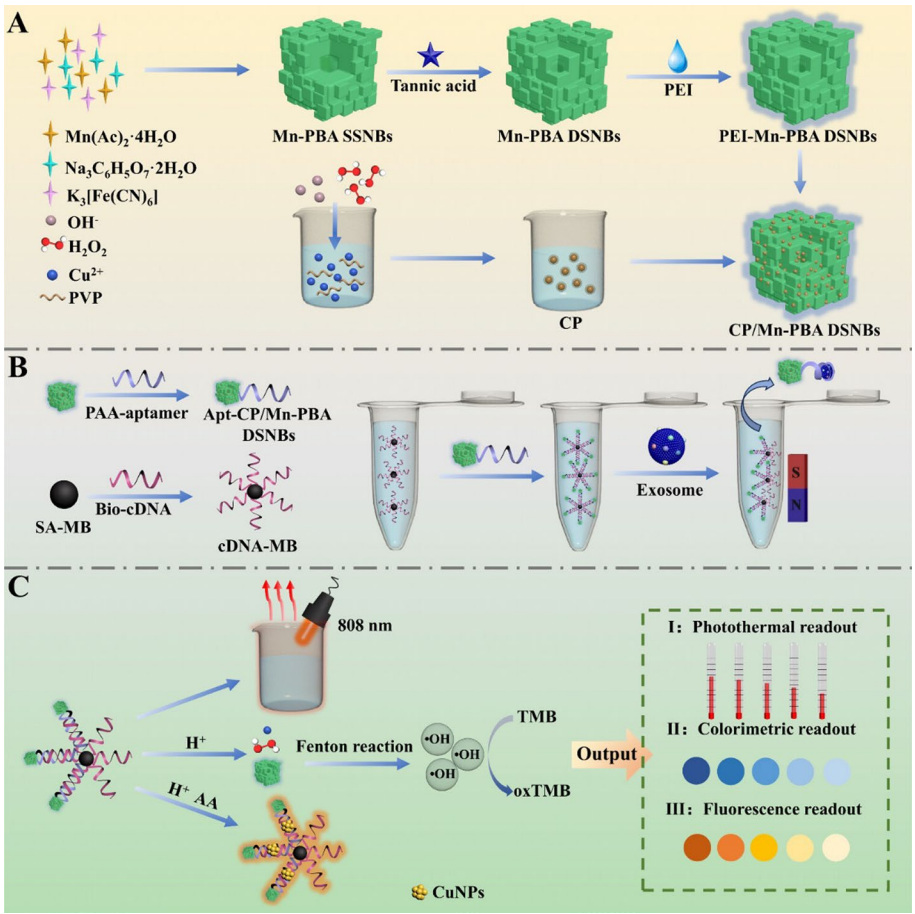

Fig. 5 Visualization of **A** the synthesis procedure of CP/Mn-PBA DSNBs, **B** the preparation steps of the aptasensor platform for gastric cancer exosome analysis, and **C** the trimode detection operation encompassing photothermal, colorimetric and fluorescence modalities [77]

and reliability for cancer cell detection, which has application potential in cancer diagnosis and treatment, and provides possibility for personalized cancer treatment. These innovative detection technologies have promoted the development of cancer research from different angles, and are expected to improve the diagnostic accuracy and treatment effect of cancer.

The development of biosensors for gastrointestinal tumor detection is full of opportunities. The improvement of detection performance is an important direction. Scientists will explore new biometric components and transducer materials, such as high-affinity nucleic acid aptamers, and use nanotechnology to create ultra-sensitive transducers to achieve accurate detection of very small biomarkers. The trend of multi-marker combined detection is obvious. Simultaneous detection of multiple biomarkers, such as miRNAs, proteins, gene mutations, etc., can more accurately assess tumor status and provide strong support for personalized treatment. For example, using a set of biomarkers can distinguish different subtypes of gastric cancer and help doctors develop more effective treatment plans. Integration and miniaturization are also worthy of attention. In the future, convenient devices will be developed to realize on-site real-time detection, which is convenient for early screening and daily monitoring. For example, wearable devices

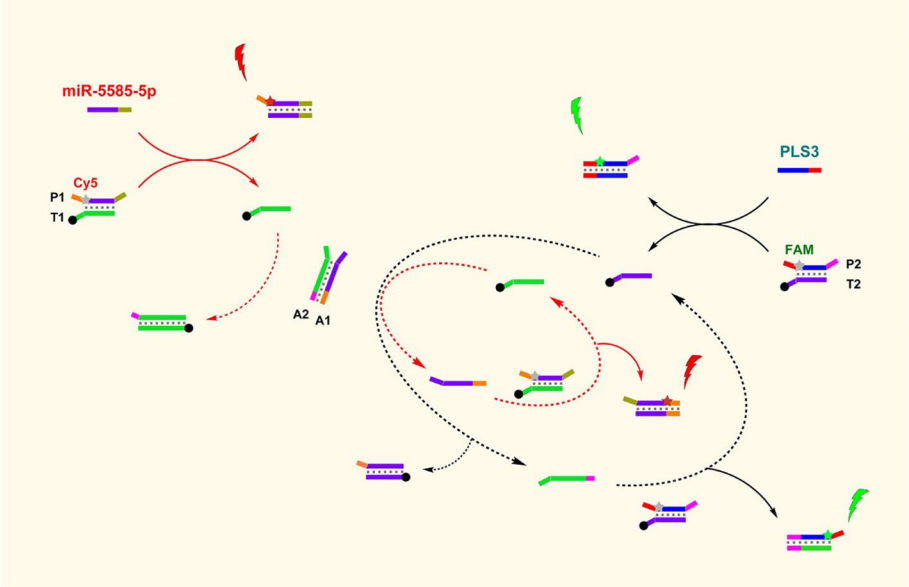

Fig. 6 Diagram of the fluorescent nanomachine that is based on the dual-biomarker-induced strand migration, single-amplification cyclic element, and DNA recycling [78]

that can detect tumor markers in sweat can detect tumor changes in time. However, the standardization of detection methods, the acceleration of regulatory approval, and the improvement of sensor stability need to be solved urgently. After breaking through these problems, biosensors will better serve the diagnosis and treatment of gastrointestinal tumors.

Summary and outlook

Biosensors have covered a variety of tumor marker detection. In colorectal cancer, there are corresponding detection technologies for different types of markers, such as nucleic acid, protein, cells and exosomes. Nucleic acid testing technology continues to innovate from miRNA to DNA-related detection, and the detection limit can reach a very low level; protein marker detection methods are diverse and have excellent performance; cell and exosome detection also provides a new perspective for disease research. In esophageal cancer detection, enzyme cascade, immune and other types of sensors have their own characteristics. Gastric cancer detection also involves miRNA, protein, cells and exosomes, and related sensors continue to emerge. These biosensors have been continuously optimized in key indicators, such as detection limit, sensitivity, and specificity, and some have been applied to clinical practice or have shown clinical application potential.

Looking to the future, biosensors are expected to make further progress in several aspects. Detection performance will continue to improve, achieving higher sensitivity, lower detection limit, and better specificity, to detect gastrointestinal tumors earlier and more accurately. Multi-marker combined detection will become a trend, through the simultaneous detection of multiple related markers, more comprehensive assessment of tumor status. In addition, the integration and miniaturization of

sensors is expected to be realized. This will enable swift on-site detection, offer more accessible means for the early screening and prompt diagnosis of diseases, and consequently contribute to a remarkable enhancement in the level of gastrointestinal tumor diagnosis and treatment.

Author contributions
C.R. and L.L. wrote the main manuscript text and F.W. prepared Figs. 1–3. All authors reviewed the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consent to the publication.

Competing interests
The authors declare no competing interests.

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