Research progress of aptamers in the diagnosis and treatment of colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths. The high incidence rate and poor prognosis of CRC pose a serious threat to public health, and impose a notable social and economic burden. Therefore, improving the accuracy of the early diagnosis and treatment of CRC is of notable importance. Aptamers have substantial potential for tumor-targeted diagnosis and treatment due to their unique advantages, such as high affinity, high specificity and programmability. In the diagnosis and treatment of CRC, aptamers can specifically target receptors on the surface of cancer cells and intervene in the development of CRC by inhibiting receptor activity. The present study reviews the current state of research on aptamers to provide a new scientific basis and methods for diagnosing and treating CRC. The relevant research achievements are organized based on the two major branches of diagnostic detection and targeted therapy to systematically assess the translational value of various CRC aptamers.

Contents

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Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; SELEX, systematic evolution of ligands by exponential enrichment; PTK7, protein tyrosine kinase 7; EMT, epithelial-mesenchymal transition; ApDC, aptamer-drug conjugate; EphA2, Ephrin type-A receptor 2; CTC, circulating tumor cell; NCL, nucleolin; IDD, intrinsically disordered domain; EpCAM, epithelial cell adhesion molecule

Key words: aptamers, CRC, diagnosis, treatment

1. Introduction

Colorectal cancer (CRC), as the third most common malignant tumor worldwide (1), has exhibited a notable upward trend in incidence and mortality in China (2). A multitude of epidemiological studies have indicated that a combination of factors, including the westernization of dietary patterns, sedentary lifestyle and population aging, have collectively contributed to the increase in CRC incidence (3-5). Furthermore, the poor prognosis of CRC poses a notable threat to public health. Consequently, the implementation of early screening, precise diagnosis and effective treatment has been identified as a pivotal strategy to mitigate the risk of CRC and enhance patient prognosis.

The early screening for CRC mainly relies on two technical systems: Colonoscopy and fecal immunochemical test (FIT). Colonoscopy, regarded as the 'gold standard' of diagnostic methods, exhibits a high degree of diagnostic value; however, it is an invasive procedure that carries inherent risks. Colonoscopy necessitates meticulous bowel preparation, encompassing dietary adjustments and the use of laxatives, and can lead to discomfort during the procedure and in the post-procedure period (6). Elderly and frail individuals have a poor tolerance to colonoscopy, and the incidence of mild adverse events such as abdominal pain, abdominal distension, diarrhea, constipation, nausea, vomiting, hematochezia, and anal and rectal pain within 48 h of the examination is relatively high (7). Although FIT has the advantage of being non-invasive, its detection sensitivity is limited by sample preservation conditions and is expensive, markedly restricting its promotion and application in primary medical institutions (8). In the treatment field, conventional chemotherapy methods, such as the FOLFOX regimen, have been demonstrated to improve patient prognoses; however, these methods frequently result in grade three or higher bone marrow suppression, with an incidence rate of ~20%. These methods can also result in cumulative dose-related neurotoxicity, immunocompromise, gastrointestinal reactions and liver damage, among other adverse effects (9). Emerging immunotherapies, such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, have shown notable efficacy (10). Objective response rates to

PD-1/PD-L1 range from 40-50% in patients with the microsatellite instability-high type cancer (11). This type accounts for 5-15% of advanced CRC; however, the applicable population is limited and the mechanism of drug resistance is unclear. Therefore, developing new screening and treatment technologies that are both highly sensitive and less invasive is still an urgent need in CRC diagnosis and treatment research.

Aptamers are a type of single-stranded oligonucleotide (DNA or RNA) that can specifically and highly interact with target molecules through the systematic evolution of ligands by exponential enrichment (SELEX) (12,13). Aptamers are known as 'chemical antibodies'; their unique spatial structure includes hairpin, G-quadruplex, G-triplex, bulge and stem-loop structures, thus resulting in a larger specific surface area compared with linear unstructured single-stranded nucleic acids, which enhances their interaction with target molecules. Compared with antibodies, aptamers have several advantages, including a small molecular weight, ease of chemical modification, low immunogenicity, strong tissue penetration (14) and lower production costs. They have broad application prospects in precision cancer medicine (15), and can be used as diagnostic tools and developed as therapeutic agents (16). Notably, compared with antibodies, therapeutic aptamers can more easily regulate the biological pathways involved in a number of diseases, including cancer, infectious diseases and cardiovascular diseases (17).

Aptamers are widely used in noninvasive imaging and targeted therapy of tumors (18), and biosensors based on aptamers show promise in tumor diagnosis and efficacy monitoring (19). An increasing number of studies have been dedicated to converting aptamers into effective clinical diagnostic and therapeutic tools (20-22). Notably, the study of CRC aptamers has established a complete chain ranging from discovery and screening (SELEX) to diagnostic applications (detection, imaging and enrichment) and therapeutic applications (targeted delivery and direct intervention). Research and application of nucleic acid aptamers targeting CRC primarily focus on two major areas: i) Early disease diagnosis and precise detection, and ii) targeted therapy and drug delivery. The following section systematically sorts representative CRC aptamers and their research progress from the two core dimensions of diagnostic detection and targeted therapy.

2. Specific research

Diagnosis and detection. This section summarizes aptamer research for early CRC identification, covering biomarker quantitative detection, liquid biopsy circulating tumor cell (CTC) capture and *in vivo* molecular imaging for tumor typing. Three subdivided research directions are classified as follows.

Ultra-sensitive detection of biomarkers. Biomarker detection based on aptamer biosensors enables trace quantification of tumor-related proteins, extracellular vesicle (EV) surface markers and tumor cell antigens, supporting early auxiliary diagnosis of CRC.

Ephrin type-A receptor 2 (EphA2) is an important member of the Ephrin/Eph tyrosine kinase receptor family; this transmembrane protein has a molecular weight of 130-140 kDa and serves a crucial role in tumor development and progression (23). EphA2 is abnormally highly expressed in various malignant tumors including colorectal cancer, lung, breast, ovarian and cervical cancers (24), and promotes tumor cell proliferation, migration and invasion by activating downstream signaling pathways such as PI3K/Akt/mTOR and MAPK/ERK (25,26). The aptamer W3, selected via SELEX technology, exhibits high specificity and affinity for EphA2, with a dissociation constant in the nanomolar range (27).

In the diagnostic application field, Chen *et al* (28) constructed a fluorescence aptamer sensor, FAM-W3-graphene oxide (GO), based on GO. Leveraging the fluorescence quenching effect of GO and the indicator function of FAM-W3, the sensor can specifically detect LoVo CRC cells in *in vitro* artificial blood samples spiked with LoVo cells with a detection limit of 10 cells/ml. This finding suggests that the system has the potential to serve as a probe for detecting CRC cells.

Epithelial cell adhesion molecule (EpCAM) is a type I transmembrane glycoprotein that is upregulated in epithelial tumors including colorectal, breast, gastric, ovarian, pancreatic and lung adenocarcinomas (29-31), which is specifically recognized by the aptamer SYL3C targeting the EGF-like domain of EpCAM. Combined with protein tyrosine kinase 7 (PTK7)-targeted SGC8 and CD63 aptamers, a multi-aptamer logic gate detection platform for serum EVs was constructed by Tan *et al* in late 2022 (32). The AND logic detection system was shown to simultaneously detect EpCAM/SYL3C, CD63/CD63-1 and PTK7/SGC8 markers on EVs from patients with CRC, achieving an area under the curve of 0.93 and diagnostic sensitivity of 92.5%. Compared with single-marker detection, the combined aptamer panel improved diagnostic specificity by 35%. This platform thus achieves ultrasensitive identification of EV surface tumor biomarkers and enhances high-accuracy early screening of CRC by distinguishing healthy volunteers and patients with CRC using clinical serum samples (33). Table I also lists biomarker-dedicated aptamers such as Seq-2, anti-D63 and J3 for trace detection of CRC-related serum markers, exosome antigens and metastatic tumor cells, respectively.

Liquid biopsy and CTC enrichment. Liquid biopsy based on peripheral blood CTCs represents a minimally invasive early screening modality for CRC, and aptamers serve as high-performance capture probes enabling specific enrichment of CTCs.

The W3 aptamer targeting EphA2 has previously been modified with a 5'-terminal FAM fluorophore and a 3'-terminal BHQ1 quencher to construct the molecular beacon MAB-W3-3G, which achieves specific identification of CTCs isolated from the peripheral blood of patients with CRC, with a clinical sample detection rate of 92% (34). Multiple independent studies have fully verified the reliability and diagnostic potential of W3-based molecular beacons for CTC capture and early CRC liquid biopsy (35,36). Nevertheless, relevant research on the therapeutic application of W3 remains insufficient. To accelerate its clinical translation, follow-up investigations need to address key bottlenecks including insufficient *in vivo* stability and unsatisfactory *in vivo* targeted delivery efficiency. As well as W3, aptamer J3, as mentioned in Table I, is capable of specific binding to metastatic LoVo CRC

Table I. Application of nucleic acid aptamers for CRC.

Aptamer	Target	Usage (Diagnosis/Treatment)	(Refs.)
PL1	CT26 cells	Treatment	(61,67)
Seq-2	Human CRC cells	Diagnosis	(68,69)
Anti-D63	CD63	Diagnosis	(18,61)
SL2B	VEGF	Treatment	(37,60)
Cs5	CD133	Treatment	(38,68)
rS3-PA	Stat3	Treatment	(18,38)
J3	LoVo cells	Diagnosis	(37,38)
CD133	HT-29 cells	Treatment	(38)

CRC, colorectal cancer.

cells (37,38), which can be utilized to enrich peripheral CTCs and assist liquid biopsy-based CRC diagnosis.

Multi-target imaging and molecular subtyping. Aptamers labeled with fluorescence or radionuclides act as molecular imaging probes to enable *in vivo* visualization of tumor lesions, distinguish molecular subtypes based on target expression level, and support staging and prognosis evaluation of CRC.

PTK7 [also known as colon carcinoma kinase 4 (CCK-4)] is an evolutionarily conserved transmembrane receptor that participates in embryonic development and tissue homeostasis by regulating the non-canonical Wnt signaling pathway. Notably, the CCK-4 gene was initially identified as being upregulated in CRC (39). Subsequent studies have confirmed that its upregulation drives tumor metastasis by promoting epithelial-mesenchymal transition (EMT) (40-43). PTK7 is currently regarded as a potential biomarker for the diagnosis and prognosis assessment of CRC (44).

The aptamer SGC8/Sgc8-c is a 41-base single-stranded DNA, which was obtained through SELEX technology screening; its G-quadruplex structure can selectively recognize the extracellular domain of PTK7, which is upregulated in CRC. Molecular imaging technology can visualize the tumor-related pathological and physiological changes *in vivo*. The core of molecular imaging is molecular probes that can accurately track tumor-specific biological events, such as PTK7 overexpression, tumor proliferation and metastasis in CRC. The aptamer Sgc8-c has been demonstrated to function as a probe for the *in vivo* diagnosis of CRC (45). For example, Arévalo *et al* (46) labeled Sgc8-c with the near-infrared fluorophore Alexa Fluor 647 and prepared a fluorescent molecular probe, Sgc8-c-Alexa 647, subsequently performing fluorescence imaging in a xenograft mouse model of CRC. The experimental study confirmed the specificity of the competition experiment. The fluorescence signals of the tumors and major organs of the model mice that were pre-injected with unlabeled Sgc8-c (Sgc8-c-NH_2) were markedly weaker than those in the experimental group receiving only Sgc8-c-Alexa 647 for competitive binding verification. These results indicated that Sgc8-c-Alexa 647 can specifically target PTK7-positive tumor tissues. In accordance with the findings of this previous study, the development of Sgc8-c as an imaging probe for CRC holds notable value and demonstrates considerable promise for future clinical application.

In early 2023, Ding *et al* (47) advanced SGC8 clinical research; its distribution and metabolism in the human body were explored and a related pharmacokinetic model was established. The researchers modified SGC8 with the chelating agent NOTA and labeled it with ^{68}Ga[Ga] to create the molecular probe ^{68}Ga[Ga]-NOTA-SGC8. Preclinical evaluations confirmed its potential for diagnosing PTK7-positive tumors (48). Subsequently, a prospective clinical trial (47) was conducted. Whole-body dynamic positron emission tomography imaging showed that, after intravenous injection, the probe circulated rapidly, completing aortic perfusion in 30 sec, entering the pulmonary vessels in 40 sec, and beginning to accumulate in the liver, spleen and kidneys in ~100 sec. Equilibrium was reached in 8 min, after which the probe was cleared by the kidneys into the bladder. Based on these data, a physiologically based pharmacokinetic model was successfully constructed, providing a foundation for the future assessment of doses and prediction of the efficacy of nucleic acid aptamer-drug conjugates (ApDC).

Targeted therapy. Aptamers can be conjugated with chemotherapeutic drugs, loaded on nanocarriers/exosomes or directly block tumor signaling pathways; they can also cooperate with immunotherapy to enhance antitumor effects.

Targeted drug delivery systems. Aptamer-modified delivery vehicles overcome the non-specific distribution of chemotherapeutics, improve tumor cell uptake efficiency, reduce systemic toxic side effects and elevate antitumor activity. i) AS1411 aptamer targeting nucleolin (NCL). NCL is a multifunctional ribonucleoprotein composed of ~700 amino acids. Its structural characteristics include two low-complexity intrinsically disordered domains (IDDs): The N-terminal IDD contains four acidic regions that mediate interactions with histones; the C-terminal IDD participates in RNA binding through RGG/FGG repeat sequences (49). The aptamer AS1411 is a single-stranded DNA aptamer rich in 26 base guanines (50,51), which binds NCL with high affinity and specificity. The AS1411-functionalized exosomal drug delivery system [doxorubicin (DOX)-Apt-Exo] developed by Hosseini *et al* (52) demonstrated notable therapeutic advantages in the human CRC HCT-116 cell line. *In vitro* experiments demonstrated that the cellular uptake efficiency of the compound was

eightfold higher than that of free DOX (P<0.001) (53), and the IC_{50} decreased from 1.2 to 0.15 μM. *In vivo* experiments confirmed that the tumor-targeted accumulation increased by 5.3 times (%ID/g), and the survival time of tumor-bearing mice was prolonged by 62%. This previous study proposes a novel strategy to overcome the non-specific distribution of chemotherapy drugs.

ii) Sgc8-c ApDC. In recent years, research on the use of the aptamer Sgc8-c for the diagnosis and treatment of CRC has increased. Most of these studies have shown that targeted drug delivery technology based on Sgc8-c is possible (54-57). For example, Li *et al* (58) constructed an Sgc8-c-artesunate conjugate via a C6-amino modification, achieving an 8:1 drug loading ratio. In a HCT-116 cell model, the IC_{50} was 0.15 μM, which was 20 times lower than the IC_{50} of the free drug (3.1 μM). This strategy leverages water solubility and targeting properties to effectively and notably overcome the problems of the poor water solubility and low cellular uptake rate of artemisinin, enhancing antitumor activity. This is important for future clinical diagnosis, treatment and prognosis assessment.

iii) SYL3C modified microemulsion nanocarriers. The SYL3C aptamer specifically recognizes EpCAM upregulation on HT-29 CRC cells (28,29). Researchers have constructed SYL3C anchored microemulsions (SYL3C/EP-MEs) co-loaded with β-bergamotene and paclitaxel (59). *In vitro* cell tests verified enhanced selective uptake, apoptosis induction and cytotoxicity against HT-29 cells. In nude mouse subcutaneous tumor models, the microemulsion markedly suppressed tumor proliferation and prolonged the survival of tumor-bearing mice. Table I lists multiple delivery-oriented aptamers: PL1 for CT26 cell-targeted delivery, SL2B targeting VEGF, Cs5 and CD133 aptamers for CRC stem cell therapy, and rS3-PA peptide aptamer combined with irinotecan for synergistic chemotherapy (18), which all belong to aptamer-modified targeted nanomedicine delivery systems.

Direct inhibition of signaling pathways. Aptamers bind target transmembrane receptors or intracellular effector proteins to block abnormal oncogenic signaling cascades, directly inhibiting tumor proliferation, migration and EMT progression. The SGC8 aptamer targets PTK7, a key upstream regulator of the non-canonical Wnt pathway. Upregulated PTK7 accelerates EMT and the distant metastasis of CRC (40,44). Notably, SGC8 competes with endogenous ligands to block PTK7 receptor activity, thereby suppressing Wnt pathway-mediated tumor invasion and metastasis. The W3 aptamer binds the EphA2 receptor and interferes with downstream proliferation and migration signal transduction (23,25). The rS3-PA peptide aptamer listed in Table I targets the Stat3 oncogenic transcription factor, directly inhibiting Stat3 pathway activation and strengthening the growth suppressive effect of irinotecan on CRC cells (18). The SL2B aptamer against VEGF can block tumor angiogenesis signaling to cut off nutrient supply for lesion growth (60).

Immunotherapy. Aptamers can also be combined with immune checkpoint inhibitors, DNA nanostructures and immunostimulants to synergistically activate antitumor immune response, representing an emerging translational direction for CRC comprehensive treatment. The PL1 aptamer has been assembled into a multifunctional DNA tetrahedron together with a Pcsk9 small interfering RNA, and this has been shown to potentiate anti-PD-L1 immune checkpoint therapy against CRC (61). The PL-1 aptamer-containing DNA tetrahedron nanostructure enables co-delivery of the targeting ligand and immune regulatory nucleic acid, relieves tumor immune microenvironment suppression and enhances the antitumor immune killing effect of anti-PD-L1 therapy. At present, research on aptamer single-agent immunotherapy for CRC is still limited (62); future research should further explore the combined application of aptamer targeting technology and PD-1/PD-L1 immune inhibitors to expand the applicable options for CRC immunotherapy (18,63).

3. Conclusions and prospects

The present review comprehensively presents the latest research progress of aptamers in the field of diagnosis and treatment of CRC. Based on the two major branches of diagnostic detection and targeted therapy specified, representative aptamers including SGC8 targeting PTK7, W3 targeting EphA2, AS1411 targeting NCL and SYL3C targeting EpCAM are systematically organized, covering three diagnostic sub-directions (ultra-sensitive biomarker detection, liquid biopsy CTC enrichment and multi-target molecular imaging) and three therapeutic sub-directions (targeted drug delivery systems, direct signaling pathway inhibition and aptamer-combined immunotherapy). These aptamers have been used in a variety of ways, including as molecular imaging probes and CTC sensors. They have also been used in targeted therapy, such as in ApDC systems and functionalized exosome drug delivery systems. In addition, they have been used in integrated diagnosis and treatment, including in a multi-aptamer logic gate detection platform. These achievements not only corroborate the intrinsic benefits of aptamers as 'chemical antibodies', namely their nanomolar affinity, low immunogenicity, programmable modifiability and cost-effectiveness for large-scale manufacturing, but also underscore their practical potential in translational medicine. In addition to the aforementioned typical aptamers, various emerging aptamers, such as candidate molecules targeting carcinoembryonic antigen and mesenchymal-epithelial transition factor (c-Met), have been explored for CRC diagnosis and treatment (64,65). The continuous expansion of the aptamer repertoire reflects the progressive diversification within this research field.

Despite the demonstrated potential of aptamers in the diagnosis and treatment of CRC, notable challenges remain to be overcome before their clinical translation can be realized. These challenges include enhancing *in vivo* stability to resist nucleases, optimizing delivery efficiency to solid tumors and reducing off-target effects. Future research endeavors should prioritize the development of more stable modification strategies. Potential strategies include engineering transformation of the framework and the encapsulation of novel nanocarriers. In addition, the design of intelligent, responsive delivery systems to improve tumor accumulation has been suggested, as has the use of advanced screening techniques to enhance aptamer specificity (59,66). Subsequent research endeavors will prioritize the efficient recognition of CRC-specific targets, such as rare mutation subtypes. These efforts will also encompass the exploration of innovative combination modes with existing

therapies, including immunotherapy, and the active promotion of high-throughput screening technologies, such as microfluidics. The continuous optimization of aptamer technology will drive its clinical translation, providing more precise and effective diagnostic and therapeutic tools for patients with CRC.

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Availability of data and materials

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Authors' contributions

YWL and PHY conceived the study and were primarily responsible for the literature search, screening, data extraction and synthesis. YWL drafted the initial manuscript. PHY, JZ and BHW contributed to the in-depth analysis and interpretation of the collected literature. ML performed literature retrieval, background data collection and Table I preparation, and critically revised the manuscript for intellectual content. BLB provided the original concept, secured funding, supervised the entire project, and critically revised and edited the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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