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Editorial Board of *World Journal of Gastroenterology*, Tzung-Hai Yen, MD, PhD, Doctor, Professor, Department of Nephrology, Clinical Poison Center, Chang Gung Memorial Hospital, Taipei 105, Taiwan.
m19570@adm.cgmh.org.tw

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Nanotechnology for colorectal cancer detection and treatment

Purnima Gogoi, Geetika Kaur, Nikhlesh K Singh

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Purnima Gogoi, Geetika Kaur, Nikhlesh K Singh, Integrative Biosciences Center, OVAS, Wayne State University School of Medicine, Detroit, MI 48202, United States

Corresponding author: Nikhlesh K Singh, DVM, PhD, Associate Professor, Integrative Biosciences Center, OVAS, Wayne State University School of Medicine, 6135 Woodward Avenue, Detroit, MI 48202, United States. nsingh2@wayne.edu

Abstract

Colorectal cancer (CRC) is the third most diagnosed cancer and the second leading cause of cancer-related mortality in the United States. Across the globe, people in the age group older than 50 are at a higher risk of CRC. Genetic and environmental risk factors play a significant role in the development of CRC. If detected early, CRC is preventable and treatable. Currently, available screening methods and therapies for CRC treatment reduce the incidence rate among the population, but the micrometastasis of cancer may lead to recurrence. Therefore, the challenge is to develop an alternative therapy to overcome this complication. Nanotechnology plays a vital role in cancer treatment and offers targeted chemotherapies directly and selectively to cancer cells, with enhanced therapeutic efficacy. Additionally, nanotechnology elevates the chances of patient survival in comparison to traditional chemotherapies. The potential of nanoparticles includes that they may be used simultaneously for diagnosis and treatment. These exciting properties of nanoparticles have enticed researchers worldwide to unveil their use in early CRC detection and as effective treatment. This review discusses contemporary methods of CRC screening and therapies for CRC treatment, while the primary focus is on the theranostic approach of nanotechnology in CRC treatment and its prospects. In addition, this review aims to provide knowledge on the advancement of nanotechnology in CRC and as a starting point for researchers to think about new therapeutic approaches using nanotechnology.

Key Words: Nanoparticles; Colorectal cancer; Carbon nanotubes; Dendrimers; Quantum dots

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Core Tip: Colorectal cancer (CRC) is the third most diagnosed cancer and the second leading cause of cancer-related mortality in the United States. Genetic and environmental risk factors play a significant role in the development of CRC. This review discusses the recent insights into nanotechnology-based methods for screening, detection and treatment of CRC. This review aims to provide knowledge on the advancement of nanotechnology in CRC and as a starting point for researchers to think about new therapeutic approaches using nanotechnology.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the United States, after lung cancer. The mortality rate of a cancer depends on its type and the sex, race and other social factors of the patient. Death from CRC affects more males than females[1]. While it is predicted that more than 1 million individuals will be diagnosed with CRC every year[2], there is a substantial geographical difference in the global distribution of CRC. The countries with the highest incidence rates of CRC are Australia, New Zealand, Canada, the United States and parts of Europe. The lowest-risk countries include China, India and parts of Africa and South America[3]. Risk factors of CRC are associated with body mass index, smoking cigarettes, red meat consumption, family history of CRC and irritable bowel disease[4], while published literature also suggests that risk of CRC decreases with physical activity, hormone therapy in postmenopausal women, aspirin/nonsteroidal anti-inflammatory drug use, fruit consumption and vegetable consumption. Thus, CRC is a disease that the management of our daily habits can prevent. Although a hereditary risk factor is involved with CRC, effective early diagnosis strategies enable earlier initiation of therapy, thereby reducing the cancer's mortality rate.

Recently, nanotechnology has gained global consideration with its great potential for diagnosing and treating CRC. Nanotechnology utilizes nanoparticles (NPs) for specific identification of tumors and cancer biomarkers, biologically targeted contrast agents, drug delivery systems and novel treatment approaches[5]. This review discusses the recent insights into nanotechnology-based methods for screening, detection and treatment of CRC.

CRC CAUSES AND STAGES

The growth of CRC incidence worldwide is related to genetic and environmental risk factors, in addition to sex, age, ethnicity, gut microbiota and socioeconomic factors[6]. Environmental risk factors include obesity, a sedentary lifestyle, poor diet, alcohol addiction, long-term smoking[7] and genetic factors due to inherited mutations or familial CRC[8]. Diet significantly impacts the microbiome environment and the risk of CRC development. Consumption of high-fiber diets and diet supplementation with polyunsaturated fatty acids, polyphenols and probiotics could potentially reduce the risk of CRC[9]. About 70% of CRC cases are sporadically seen among patients over age 50, mainly due to dietary and environmental factors[10]. In addition, a family history of CRC and a personal history of chronic inflammatory bowel disease, type 2 diabetes, or genetic diseases like familial adenomatous polyposis or Lynch syndrome are related to augmented risk[11]. Acquisition of genetic and epigenetic mutations in specific oncogenes and tumor suppressor genes in normal epithelial cells leads to the sequential transformation of the normal colorectal epithelial cell into adenocarcinoma[12]. Chromosomal instability, microsatellite instability and CpG island methylator phenotype are primary pathways influencing development of CRC[13].

The stages of CRC determine the survival rate. Around 90% of CRCs are stage I, while 10% of the cases are diagnosed with stage IV metastasis, implying that early diagnosis leads to high chances of survival[14]. The tumor stage determines whether the therapy is beneficial and how successful the treatment might be against CRC[15]. The stages of CRC range from stage 0 to IV depending on the progression of cancer across the layers of the colon and rectum, effect on lymph nodes or nearby tissues, or its metastasis to distant organs (Table 1)[16]. Out of all the stages, stage IV CRC is not often curable, but it can be managed based on the cancer's growth and spread[17]. The sequential steps in CRC carcinogenesis are presented in Figure 1.

Table 1 Stages of colorectal cancer development and progression

Stage	Progression	Metastasis
0	Unusual abnormal cells arise from mucosa of the colonic wall, eventually becoming cancerous and known as carcinoma <i>in situ</i> or intramucosal carcinoma	No
I	Cancerous cells spread from the mucosa to submucosa and may also extended until the muscularis propria	No
II		
IIA	Cancerous cells spread out from the submucosa to serosa (outermost layer) of the colon wall	No
IIB	Cancerous cells spread through serosa but are not extended to nearby organs	No
IIC	Cancerous cells spread to nearby organs	No
III		
IIIA	In the first case, cancerous cells grow through the mucosa into submucosa and also may extended until the muscularis propria. The cancer spread to 1 to 3 nearby lymph nodes or into the areas of fat near lymph nodes but not to distant sites In the second case, the cancer has spread through the mucosa into submucosa and has spread to 4 to 6 nearby lymph nodes	No
IIIB	In the first case, cancerous cells have spread through the muscularis propria of colon and/or rectum up to serosa or through the serosa to tissues and visceral peritoneum. They have also spread to 1 to 3 nearby lymph nodes or cancer cells are present in nearby tissues of lymph nodes but have not spread to distant sites Second case, the cancer has spread into the muscularis propria or into the outermost layers of colon or rectum and has spread to 4 to 6 nearby lymph nodes but not to distant sites Third case, the cancer has spread through the mucosa into submucosa and it might also have grown into the muscularis propria of colon and/or rectum and has spread to 7 or more nearby lymph nodes but not to distant sites	No
IIIC	First case, the cancer has grown through the serosa colon and/or rectum to visceral peritoneum but has not reached nearby organs. It has spread to 4 to 6 nearby lymph nodes but not to distant sites Second case, the cancer has grown into the outermost layers of the colon and/or rectum or through visceral peritoneum but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes but not to distant sites Third case, the cancer has grown through the wall of the colon and/or rectum and is attached to or has grown into other nearby tissues or organs. It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes but not to distant sites	No
IV		
IVA	The cancer has spread to one area or organ that is not near the colon and/or rectum, may be liver, lung, ovary, or a distant lymph node	Yes
IVB	The cancer has spread to more than one area or organ that is not near the colon and/or rectum, such as the liver, lung, ovary, or a distant lymph node	Yes
IVC	The cancer has spread to the tissue that lines the wall of the abdomen and may have spread to other areas or organs	Yes

CURRENTLY AVAILABLE METHODS OF CRC DETECTION

The United States Preventive Services Task Force recommends colorectal screening for adults aged 45 to 75. Several techniques are used to detect polyps or CRC, but colonoscopy is a must to confirm the screening process and other screening tests. The most used methods for screening CRC are stool test, flexible sigmoidoscopy, colonoscopy, computed tomography colonography and double-contrast barium enema[18-28] in Table 2. Detection of DNA biomarkers is a promising technique for CRC screening. Stool-based DNA markers are convenient and easy to use. For early detection of CRC, biomarkers such as *ITG4* methylation, *SFRP2* methylation, miR-21, miR-92a and miR-135b, as well as Cologuard® (Exact Sciences Corp., Madison, WI, United States), can be used. For malignancy detection, biomarkers such as *SFRP2* methylation, *VIM* methylation, *TFPI* methylation, miR-21, miR-92a and miR-223 can be used[29].

Clinical trials reported that sigmoidoscopy[30] and colonoscopy[31] reduce the chances of incidence and mortality of CRC. Sigmoidoscopy has a sensitivity and specificity of 92%-97% for the detection of polyps and expanded CRC and can be used to diagnose and treat CRC in patients who are ineligible for surgery (according to the severity of the tumor or comorbidities)[29]. The mentioned screening techniques detect either abnormal blood, antibodies, hemoglobin, DNA markers in the stool, or any polyps in the colon or rectum wall. Besides this, circulating tumor cell (CTC) detection-based diagnostic technology is also available, including CellSerech® assay (Janssen Diagnostics, LLC, South Raritan, NJ, United States), followed by faster and more efficient diagnostic systems like MagSweeper (Illumina, San Diego, CA, United States), Cynvenio (Cynvenio Biosystems Inc., Westlake Village, CA, United States), IsoFlux (Fluxion Biosciences, Alameda, CA, United States), VeriFAST, AdnaGen and magnetic sifters[5]. Most current screening methods of CRC are costly and not accessible at the point of care. Therefore, developing a more sensitive, fast, low-cost and specific screening test for CRC is essential.

Table 2 Screening methods for colorectal cancer

Ref.	Screening methods	
[18-20]	Stool tests	Kit-based technique; guaiac-based fecal occult blood test uses guaiac to detect heme; FIT uses antibody to detect hemoglobin in stool; FIT-DNA test detects hemoglobin and DNA biomarkers in the stool Non-invasive, low cost, colon cleansing is not required, non-bleeding tumors cannot be detected
[21, 22]	Flexible sigmoidoscopy	Flexible tube with light, lens for viewing and tool for removing tissue; rectum and lower third of the colon screened to detect polyps, cancer or other abnormalities Sedation is required; accurate detection if polyps and cancers are present; unable to detect polyps or any abnormalities present in cecum, ascending colon hepatic flexure, or on transverse colon; colon cleansing is required
[23, 24]	Colonoscopy	Flexible tube light with a lens for seeing and a tool for excising the abnormal tissue; entire colon and rectum are screened for cancer by inserting the colonoscope through anus Sedation is required; visualization of entire inner lining of the colon and rectum; minute polyps can be detected; sedation may lead to bleeding or tear of the intestinal wall; sedation may lead to bleeding or tear of the intestinal wall
[25-27]	Computed tomography colonography	X-ray based computed tomography scanner captures two- and three-dimensional images of the entire colon; computer assembles these pictures into detailed images Sedation is not required in this method; non-invasive; colon cleansing is not essential; may miss small polyps
[28]	Double-contrast barium enema	X-ray images are then captured by introducing barium sulphate enema Examination of the whole colon and the rectum; sedation is not required; for the patient who cannot undergo standard colonoscopy, this method is useful; colon cleansing is very necessary for this method; otherwise, it will give false positive results

FIT: Fecal immunochemical test.

CURRENTLY AVAILABLE THERAPIES FOR CRC TREATMENT

CRC care entails a multidisciplinary approach as the treatment options depend on factors such as the patient's age, comorbidities, overall health, type and stage of cancer, possible side effects of treatment regimens, *etc*[32]. Based on these characteristics and risk factors, patients are grouped into the following four categories for treatment guidance: (1) Group 0, no metastatic disease or relapse; (2) Group 1, potentially resectable metastatic disease; (3) Group 2, disseminated unresectable disease; and (4) Group 3, unresectable disease and unavailability of intensive or sequential treatment.

Surgery

Surgery is considered the most common treatment for CRC. It demarcates the removal of the tumor clinically during an operation. This is also called surgical resection. Group 0 patients fall under this category. Depending upon the size and location of the tumor, the surgical options include laparoscopic surgery, colostomy and radiofrequency ablation or cryoablation. Laparoscopic surgery is an effective method that is carried out by passing several scopes into the abdomen *via* smaller incisions, whereas colostomy is a surgical opening for waste removal (into a pouch) by connecting the colon to the abdominal surface. When radiofrequency waves are used to heat or freeze the malignant tumors in the liver and lungs of CRC patients, then it is called radiofrequency ablation or cryoablation, respectively [33].

Radiation therapy

In radiation therapy, the size of the tumor is reduced and cancer cells are destroyed using high-energy radiations such as X-rays, radio waves and protons. This therapy is primarily used in patients at risk of tumor recurrence. Different types of radiation therapies include external-beam, stereotactic, intraoperative and brachytherapy[34]. The difference lies with the dose and the location of the cancer. For instance, external-beam radiation therapy is usually given 5 d a week for several weeks, whereas stereotactic radiation therapy delivers precise radiation to a small area. Stereotactic radiation therapy is given in malignant cancers that spread from the colorectal region to the liver or lungs. Further, intraoperative radiation therapy and brachytherapy are specialized radiation therapies applicable only in small areas of cancer that cannot be removed by surgery. In intraoperative radiation therapy, a single and high dose of radiation is given, whereas radioactive "seeds" are used and placed inside the body in brachytherapy. Lastly, neoadjuvant therapy shrinks the tumor for easier removal through surgery[35].

Therapies using medications

Medications are given as treatment plans to destroy cancer cells or reduce the tumor size. It can be delivered systemically *via* the bloodstream or directly through intravenous injections, pills, or capsules.

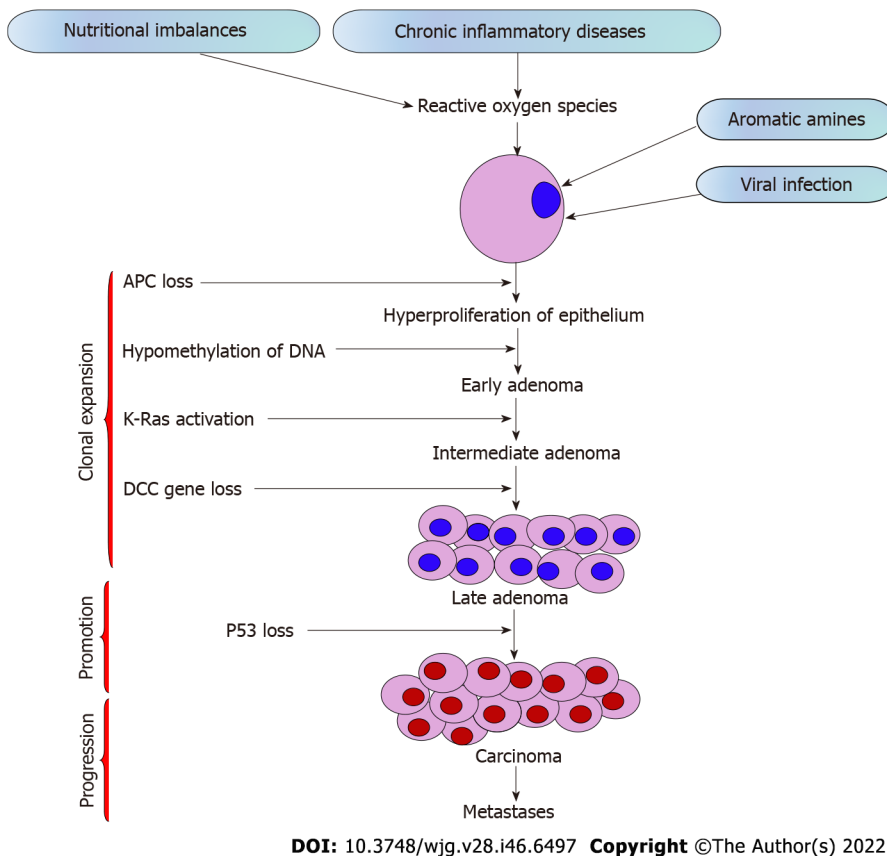


Figure 1 Schematic diagram representing the sequential steps in colon carcinogenesis. APC: Adenomatous polyposis coli; DCC: Deleted in colon carcinoma; Ras: Rat sarcoma.

Medications include chemotherapy, targeted therapy and immunotherapy[36]. Chemotherapy is generally given to group 1 patients. It is considered a central treatment strategy for all types of cancers. The United States Food and Drug Administration (FDA)-approved drugs to treat CRC are capecitabine (Xeloda[®]), fluorouracil (5-FU), irinotecan (Camptosar[®]), oxaliplatin (Eloxatin[®]) and trifluridine/tipiracil (Lonsurf[®]). For combined therapies, the combination of 5-FU with leucovorin (folinic acid), or leucovorin and oxaliplatin, or leucovorin and irinotecan, or capecitabine with irinotecan or oxaliplatin are used in group 3 patients for the treatment of CRC[37]. Different medications have different mechanistic pathways through which they act upon the cancer cells, *viz.*, inhibition of DNA replication, interference in chromosomal separation in the cell cycle, or cytotoxicity. However, chemotherapy may attack healthy cells. Chemotherapy is often given with radiation therapy to increase the effectiveness of the treatment regimen. A combination of chemotherapy and radiation is known as chemoradiation therapy. Chemoradiation therapy is often given to reduce the risk of colostomy or cancer recurrence.

Target therapy

In targeted therapy, specific genes, proteins, or a niche is targeted to hinder the growth and survival of cancer cells. It limits damage to the healthy cells in group 1 and 2 patients. The targeted therapies for treating CRC include antiangiogenesis therapy and epidermal growth factor receptor inhibitors[38,39]. As the name suggests, the role of antiangiogenesis therapy is to stop angiogenesis, *i.e.*, the formation of new blood vessels. In the tumor niche, the nutrients are provided by blood vessels for the growth of tumor cells. However, these antiangiogenesis therapies lead to the starvation of tumor cells. For example, bevacizumab (Avastin[®]), regorafenib (Stivarga[®]), ziv-aflibercept (Zaltrap[®]) and ramucirumab (Cyramza[®]) are currently used targeted drugs. The FDA approved bevacizumab and chemotherapy as the first-line treatment for CRC in 2004[40].

On the other hand, epidermal growth factor receptor inhibitors such as cetuximab (Erbix[®]) and panitumumab (Vectibix[®]) are considered adequate for group 2 patients[41]. These drugs are specific for genes like *Ras* and *Raf* and are ineffective in cases with mutations[42,43]. Other nonspecific cancerous medications such as larotrectinib (Vitrakvi[®]) and entrectinib (Rozlytrek[®]) are also used. These medications act on a specific genetic change called an neurotrophic tyrosine receptor kinase fusion. The currently available treatment methods for CRC and their side effects are detailed[32-34,36,38,39,44-47] in Table 3.

Table 3 Currently available colorectal cancer treatment methods

Treatment methods	Types/medication details	Side-effects	Stages	Ref.
Surgery	Laparoscopic surgery	Pain; tenderness; irritation and itching; constipation or diarrhea	I, II, III, IV	[32, 44]
	Colostomy for rectal cancer			
	Radiofrequency ablation or cryoablation			
Radiation therapy	External-beam radiation therapy	Fatigue; mild skin reactions; bleeding in stools; constipation or diarrhea; infertility	II, III, IV	[33, 34]
	Stereotactic radiation therapy			
	Intraoperative radiation therapy			
	Brachytherapy			
Chemotherapy	Capecitabine (Xeloda)	Vomiting; nausea; diarrhea; mouth sores; neuropathy; fatigue; hair loss	II, III, IV	[36, 39]
	Fluorouracil			
	Irinotecan (Camptosar)			
	Oxaliplatin (Eloxatin)			
	Trifluridine/tipiracil (Lonsurf)			
Targeted therapy	Anti-angiogenesis therapy	Rashes	IV	[38, 45]
	Epidermal growth factor receptor inhibitors			
	Combined targeted therapies			
	Tumor-agnostic treatment			
Immunotherapy	Pembrolizumab (Keytruda)	Fatigue; rashes, pain and itching; diarrhea; nausea; fever; vomiting; shortness of breath	III, IV	[46, 47]
	Nivolumab (Opdivo)			
	Dostarlimab (Jemperli)			
	Nivolumab and ipilimumab (Yervoy) combination			

NANOTECHNOLOGY FOR CRC DIAGNOSIS AND TREATMENT

NPs were first reported as drug carriers in 1986 and it was shown that they accumulate in tumoral tissues. This passive accumulation of NPs, known as the “enhanced permeability and retention” effect, was one of the turning points of cancer treatment using NPs. Therefore, due to their high specificity, accumulation in tumor sites and prolonged blood circulation time, NPs are considered promising for cancer therapeutics[48,49] (Figure 2). Various families of organic and inorganic NPs are available today with a vast variety of sizes, structures and compositions[49] (Figure 3). Some of the common NPs that are used for CRC diagnosis and treatment are listed here.

Iron oxide nanocrystals

Iron oxide is popular as a diagnostic and therapeutic tool for its use in oncology. The superparamagnetic properties of iron oxide NPs have attracted attention for their biomedical applications, arising due to their biocompatibility and non-toxicity[50,51]. The diameter ranges from 1-100 nm with a magnetic core to the iron oxide nanocrystals and a polymer covering containing the various medicinal molecules. These NPs have diverse biological properties due to their relatively small dimension, minimal deposition rate, efficient surface region and ease of cellular transport. Iron oxide NPs loaded with 5-FU with magnetic hyperthermia effectively reduce tumor growth in heterotopic human colon cancer in mice[52]. Epirubicin-5TR1 aptamer-superparamagnetic iron oxide NP (SPION) tertiary complex could efficiently deliver epirubicin to C26 murine colon carcinoma cells and allows tumor detection by magnetic resonance imaging (MRI)[51]. Chitosan-coated iron oxide enhanced reactive oxygen species’ production in a human colorectal carcinoma cell lines (HCT 116) and cell death was caused *via* caspase 9/3 activation[53].

Quantum dots

Quantum dots are nanocrystal particles of semiconductors ranging from 2-10 nm, with fluorescence emission affected by particle size. With its optical and chemical advantages, quantum dot-based

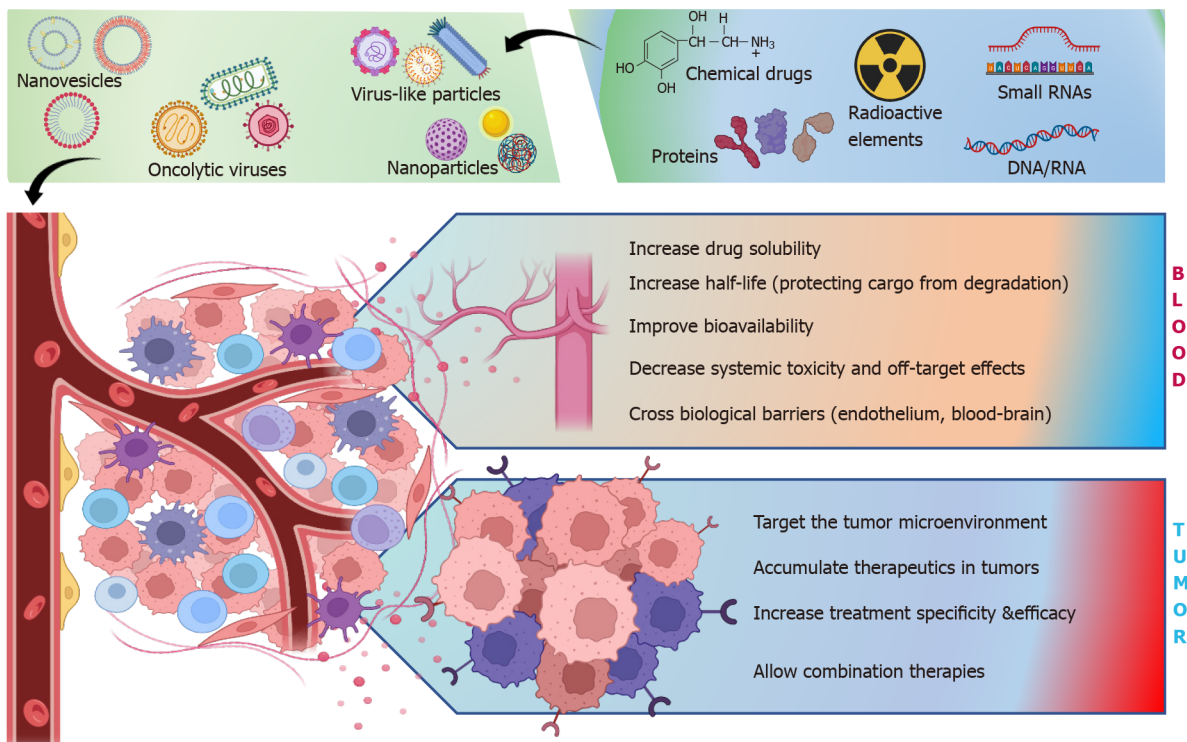


Figure 2 Advantages of nanoparticles in cancer drug delivery. Nanoparticles along with extracellular vesicles or viruses improve the clinical efficacy of various therapeutic molecules (nucleic acids, antibodies, drugs, radionuclides) with efficient delivery of these molecules to the tumor with minimal off-targeting. Nanoparticles enhance the transport of these molecules by increasing their solubility, bioavailability and half-life in the bloodstream. The tumor delivery of therapeutic molecules is also enhanced by nanoparticles, leading to their accumulation and thus potentiating the use of various combination therapies for colorectal cancer. Citation: Briolay T, Petithomme T, Fouet M, Nguyen-Pham N, Blanquart C, Boisgerault N. Delivery of cancer therapies by synthetic and bio-inspired nanovectors. *Mol Cancer* 2021; 20: 55. Copyright© The Author(s) 2021. Published by Springer Nature. The authors have obtained the permission for figure using from the Springer Nature Publishing Group ([Supplementary material](#)).

nanotechnology is a growing platform for cancer research, particularly CRC. Quantum dots are preferred for biomedical imaging due to their high quantum efficiency, photostability, extended excitation wavelengths and narrow emission band[54,55]. Various *in vitro* and *in vivo* studies have used quantum dots as fluorescent markers for cancer, with their *in vivo* use limited to nontargeted or xenograft labeling[56,57]. Vascular endothelial growth factor receptor 2 (VEGFR2) is upregulated in CRCs and QDot655 targeted to VEGFR2 (QD655-VEGFR2) showed its ability to detect VEGFR2-expressing tumors *in vivo*[58].

Poly (lactic-co-glycolic acid) NPs/nanocells

Amongst the natural and synthetic polymeric NPs, poly (lactic-co-glycolic acid) (PLGA) has been used for oral drug delivery applications approved by the United States FDA. PLGA NPs are physically and chemically stable, have higher stability in biological fluids and protect encapsulated drugs from enzymatic degradation. In addition, PLGA NPs can entrap small macromolecules, enhance thermal stability of the molecules and help in sustained release[59,60]. Due to its biodegradability and biocompatibility characteristics and its ability to encapsulate hydrophobic and hydrophilic drugs, PLGA is often used as a drug carrier[61,62]. PEGylated-PLGA nanocapsules loaded with docetaxel and SPIONs treated tumor growth in CT26 colon cancer[63]. Encapsulated 5-FU into PLGA NPs reduced the proliferation rate of the colon cancer cell line HT-29 by increasing the intracellular concentration of drugs in cancer cells[64]. EGF-functionalized PLGA NPs loaded with 5-FU and perfluorocarbons inhibited colon tumor growth[65]. The single-step surface-functionalizing technique was used to prepare PLGA/PLA-PEG-FA NPs to incorporate 17-AAG (NP-PEG-FA/17-AAG), which improved the oral bioavailability of 17-AAG and effectively treated ulcerative colitis and associated cancer[66]. 5-FU-loaded PHBV/PLGA NPs are a promising nanodrug delivery system for the treatment of colon cancer[67].

Dendrimers

Dendrimers are highly branched spherical molecules having three-dimensional chemical structures, being enormously useful in nanopharmaceuticals due to their biodegradable backbones. The versatility of dendrimers in the delivery of anticancer drugs and theranostic applications in cancer therapy has been well established. Anticancer conjugated dendrimers can deliver the drug intracellularly, bypassing the efflux transporter and improving the bioavailability of loaded molecular cargo. They are also used

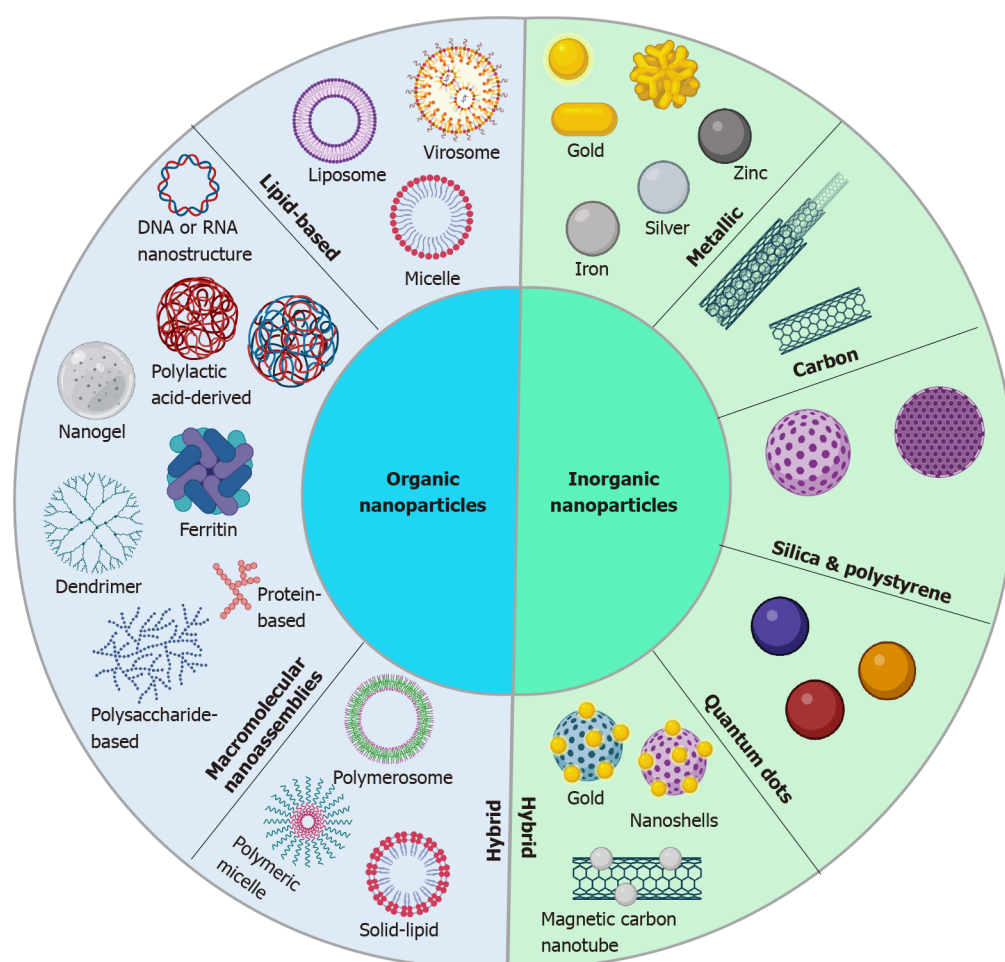


Figure 3 Inorganic and organic nanoparticles for cancer detection and therapy. The nanoparticles are divided into inorganic and organic nanoparticles. Inorganic nanoparticles, such as quantum dots, silica, carbon and metallic nanoparticles, are characterized by intrinsic electrical and optical properties suitable for cancer imaging, high stability and low biodegradability for theranostics. Organic nanoparticles, such as macromolecular assemblies or lipid-based nanoparticles, have lower stability but higher biocompatibility and multiple possibilities to add functional groups for drug delivery. Hybrid nanoparticles combine the qualities of both organic and inorganic nanoparticles to enhance their strength and biocompatibility. Citation: Briolay T, Petithomme T, Fouet M, Nguyen-Pham N, Blanquart C, Boisgerault N. Delivery of cancer therapies by synthetic and bio-inspired nanovectors. *Mol Cancer* 2021; 20: 55. Copyright© The Author(s) 2021. Published by Springer Nature. The authors have obtained the permission for figure using from the Springer Nature Publishing Group (Supplementary material).

for delivering diagnostic agents for tumor-targeted imaging[68,69].

The chemotherapeutic approach to treat CRC is not proven to be effective, as only a tiny fraction of the drug reaches the tumor target site at an effective concentration[70]. The CTCs are cancer cells that migrate and are primarily responsible for tumor metastasis. Given the importance of CTCs as an indicator of poor prognosis, several technologies (such as size-based filtration, microfluidics-based, *etc*) were utilized to isolate and capture CTCs from large populations of interfering cells but were not truly successful. Various methods were employed to detect colorectal CTC using dendrimers conjugated with antibodies, such as PAMAM dendrimers conjugated with Sialyl Lewis X antibodies to capture colon cancer HT29 cells[71].

Apart from diagnostic use, dendrimers are also reported for use in anticancer therapy *in vitro*. G4 PAMAM dendrimers conjugated with capecitabine reported decreased tumor size and reduced side effects of capecitabine[72]. Gold NPs inside PAMAM dendrimer conjugated with curcumin showed higher cellular uptake, internalization and cytotoxicity in C26 and HT29 colorectal cells[73]. Camptothecin-loaded PEGylated PAMAM dendrimer functionalized with AS1411 (anti-nucleolin aptamers) for site-specific targeting of CRC cells[74] and L-lysine dendrimers with polyoxazoline conjugated with SN-38 (the active metabolite of irinotecan) increased efficacy and it minimized adverse side effects[75]. PAMAM G4 dendrimers with oxaliplatin enhanced targeting efficacy towards folic acid receptor-expressing CRC cells *in vitro*[76]. Gemcitabine-loaded YIGSR-CMChT/PAMAM dendrimer NPs induced targeted mortality on HCT-116 cancer cells[48].

Carbon nanotubes

Carbon nanotubes (CNTs) are carbon nanomaterials with multifaceted roles in diagnosis, gene therapy, immunotherapy and a carrier in the drug delivery system. They have excellent optical properties,

thermal conductivity, chemical stability and functionalization. CNTs are tiny tubular carbon atoms ordered to form a honeycomb nanostructure with exceptional physicochemical properties[77]. Based on the sheets of carbon atom numbers, CNTs are divided into single-wall CNTs or multi-wall CNTs. Various researchers have reported the effectiveness of CNT in cancer treatment and diagnosis. CpG-conjugated CNTs elevate the CpG uptake in mouse colon cancer cells and activates nuclear transcription factor-kappa B signals. CpG-CNT conjugation successfully attenuated local xenograft tumor growth and liver metastasis[78]. Fluorescein functionalized single-walled CNT/II-NCC hybrids showed higher intrinsic activity against colon cancer cells (Caco-2) compared to the non-functionalized counterpart [79]. Single-wall CNT-conjugated antibody C225 binds to epidermal growth factor receptor-expressed CRC cells *via* receptor-mediated endocytosis[80]. Photodynamic therapy enhanced the ability to kill colon cancer cells by single-walled CNT nanobiocomposites[81].

Liposomes

Liposomes are artificial and non-toxic lipid-based vesicular carriers. Historically, liposomes were first introduced as nanocarriers in 1961 as an FDA-approved drug delivery system. It comprises a phospholipid bilayer structure with a small and spherical aqueous core[82]. The main characteristic and advantage of NPs is their smaller size, which favors the particle for effective and targeted delivery of the drug used to diagnose and treat the disease[83]. Moreover, these particles have minor side effects. Among several NPs, liposomes are primarily used for the delivery system for nucleic acids, proteins and peptides. Depending on the acting properties of liposomes, there are three types, as follows: (1) Stealth or long-circulating; (2) Active targeting; and (3) Thermo-sensitive/pH-sensitive/magnetic liposomes[84]. For example, doxorubicin (Doxil), DaunoXome and Marqibo® are FDA-approved liposomal drugs and Thermodox® is a thermo-sensitive liposome used to treat CRC[85].

Silica NPs

Silica NPs possess a beehive-like porous structure with adjustable sizes of cavities ranging from 50-300 nm and 2-6 nm[86]. The advantageous characteristics of silica NPs include a highly porous framework, less toxicity, biocompatibility, pH sensitivity and easy functionalization[87]. It is highly recommended for precise drug delivery for anticancer activity. For instance, a mesoporous silica NP-protamine hybrid system and conjugated hyaluronic acid to silica NPs load more medicine and increase the drug's efficacy in the tumor niche. For CRC, silica NPs, along with photosensitizer chemicals, are used. The photosensitizers become activated when exposed to light, releasing reactive oxygen molecules to kill the cancer cells[88].

Gold NPs

Gold NPs are considered the most stable among all noble NPs. They can be nanostructured in the form of cubes, spheres, rods, flowers, branches, wires, pyramids, shells and cages. With accurate surface coating, the gold NPs are safer, efficient for drug delivery and specific for cancer targeting[89]. Gold NPs enhanced cisplatin delivery efficacy and effectively decompressed CRC vessels[90]. Like nanoemulsion, gold NPs can also be conjugated with several molecules, such as antibodies, nucleic acids, proteins, enzymes and fluorescent dyes. These factors augment the properties of gold NPs, including stability, biocompatibility and functionalization in the medical field[91].

Nanoemulsion system

As the name suggests, a nanoemulsion system consists of oil, water and surfactant, formulating a transparent colloidal solution. It possesses the characteristics of less toxicity, high stability, thermo-sensitivity, pH-sensitivity and better efficacy[82]. Nowadays, antiangiogenic drugs have been used to target CRC cells. However, these agents cause toxicity and resistance and are affected by barriers. In the tumor niche, vascularized tissue is a barrier that nanoemulsions can easily overcome to target cancer cells[92]. Nanoemulsion systems are used to deliver water-insoluble drugs with a hydrophobic core. For effective drug delivery and treatment activity, nanoemulsions are conjugated with different antibodies for selective and specific targeting. Other than antibodies, nanoemulsions are also conjugated with polyethylene glycol. Polyelectrolyte complex micelles and DNA complexes enhance their ability as cancer therapeutics. Tween-80 is a widely accepted and used emulsifier[93].

Other NPs

In traditional cancer treatments, the therapeutic agents affect the immune system adversely, eliciting several side effects. Nanodrug delivery systems encapsulate the therapeutic agents, followed by targeted drug delivery in the tumor niche, which decreases the side effects. These systems not only lower the toxicity in the body but are highly stable, biocompatible and efficient [*e.g.*, polypeptide-based copolymers, poly(trimethylene carbonate)-block-poly(L-glutamic acid) derived polymersomes, plitidepsin-unloaded polymersomes, near-infrared fluorescent proteinoid-poly(L-lactic acid), P(EF-proteinoid-poly(L-lactic acid)) random copolymer, proteinoid-proteinoid-poly(L-lactic acid) copolymer, *etc.*]. Several copolymers are effective against CRC cells and do not elicit any side effects. Nanoformulation of curcumin in micelles, nanogels, liposomes, NPs and cyclodextrins has been documented for

treating CRC[94].

COMBINED NANOTECHNOLOGY-BASED APPROACHES FOR CRC DETECTION AND TREATMENT

With the advent of nanotechnology-based approaches, cancer detection and treatment strategies have changed in recent years. However, the clinical applications of nanotechnology-based formulations are limited due to their complex pharmacokinetics. The following are the combinatorial usage of nanotechnology-based approaches in the theranostics of CRC.

Enhancement of imaging techniques

Nanotechnology-based contrasting agents are used to enhance the capability of cancer diagnostic imaging modalities such as positron emission tomography (PET), MRI and other optical imaging techniques. The primary aim of this new technology is to detect the smallest possible number of cancer cells. PET is a powerful tool in diagnosing cancer due to its high sensitivity. A variety of relevant biomarkers are used for molecular and metabolic imaging with PET, such as fluorodeoxyglucose, ^{99m}Tc-labeled polyethylene glycol, [18F] DCFPyL, *etc.* Recently, NP-based contrasting agents including ⁵⁶Fe and ¹⁴C conjugated with SPIONs, ^{99m}Tc-radiolabeled nanosilica system conjugated with a trastuzumab half-chain and MUC1 aptamer conjugated mesoporous silica NP have been used as radiolabeled tracers for PET. PET scan does not provide anatomical information; thus, other modalities such as computed tomography or MRI are used or have been merged with PET. In the case of MRI, SPIONs, gadolinium-encapsulated silicon microparticles and gadolinium-ion-doped upconversion NPs are mainly used as contrast agents. At the same time, 2-deoxy-d-glucose labeled gold NPs and iodinated gold nanoclusters (AuNCs-BSA-I) are used in computed tomography. The advent of nanotechnology has made advancements in the imaging modalities for early detection of cancer and thus timely treatment for cancer[95].

Combined drug delivery

The primary functional role of nanotechnology in the cancer field is drug delivery. The issues of multidrug resistance, stability, efficacy and biocompatibility have been improved by formulating the drug delivery system using NPs. Traditionally, chemotherapy and other therapies have significant side effects, which are also reduced with the implementation of the nanotechnology-based formulation. For instance, 5-FU nanoencapsulation, forming a combinatorial nanomedicine agent with thiolated chitosan, is non-toxic and has enhanced chemotherapeutic efficacy in CRC patients. The use of nanomedicine has also led to a reduction in the dose quantity. In conventional therapy of 5-FU, the dose was much higher and toxic compared to nanoencapsulation of 5-FU[96].

CONCLUSION

There has been significant advancement in the field of nanomedicine over the last decade. Nanotechnology is gaining immense importance because of its highly efficient delivery system. The enormous use of nanomaterials for disease diagnosis and treatment is on-trend currently. The NP-based approaches for colon cancer diagnosis are summarized[97] in Figure 4. The combined therapy with diagnosis, *i.e.*, theranostic application of nanomaterials, makes treatment easier and faster. CRC is mainly associated with lifestyle, sex and race, suggesting that certain groups are highly vulnerable. Thus, regular screening of CRC seems to be highly recommended to prevent the occurrence of CRC. Early diagnosis of CRC increases the chances of curing cancer and survival. Theranostic application of nanomaterials against CRC is still in development. Several researchers have already reported the successful treatment of CRC *in vitro* in cancer cell lines and *in vivo* in various CRC model animals. However, new strategies are required to improve the pre-existing therapeutics and hopefully novel therapeutics using nanomaterials to treat CRC will be available soon for clinical application.

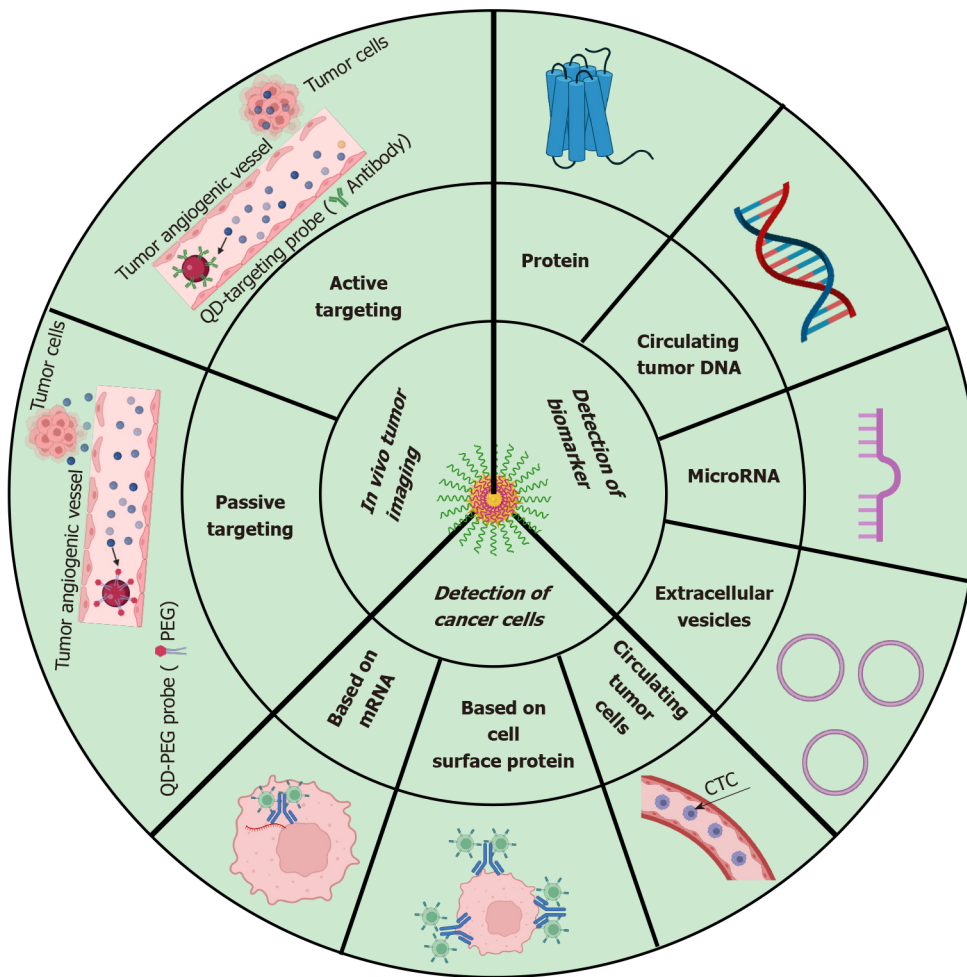


Figure 4 Schematic diagram representing the nanotechnology-based applications in colon cancer diagnosis. CTC: Circulating tumor cell; PEG: Polyethylene glycol; QD-PEG: Quantum dots-polyethylene glycol. Citation: Zhang Y, Li M, Gao X, Chen Y, Liu T. Nanotechnology in cancer diagnosis: progress, challenges and opportunities. *J Hematol Oncol* 2019; 12: 137. Copyright© The Author(s) 2019. Published by Springer Nature. The authors have obtained the permission for figure using from the Springer Nature Publishing Group (Supplementary material).

FOOTNOTES

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ORCID number: Nikhlesh K Singh 0000-0002-3665-6023.

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