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Precision nanomaterials in colorectal cancer: advancing photodynamic and photothermal therapy

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Nanomaterials, due to their unique size, excellent targeting ability, and good biocompatibility, have gradually gained attention in oncologic medical treatments. Photodynamic therapy (PDT) and photothermal therapy (PTT), known for their low side effects and minimal trauma, are widely used in immunotherapy for malignant tumors. However, limitations such as low light penetration depth, poor targeting, and localized thermal effects restrict the application scope of photothermal dynamic therapy. Clinical studies have found that nano-mediated targeted drug carriers exhibit low toxicity and good biocompatibility. Furthermore, the superior photothermal conversion performance of nanomaterials can significantly enhance the efficacy of photothermal dynamic therapy in colorectal cancer treatment. Nanomaterials, which have been involved in various cancer treatment processes, represent an emerging medical biomaterial. This review systematically explores the types of nanomaterials currently commonly applied in medicine, with a particular focus on their breakthroughs and cutting-edge research in photodynamic therapy (PDT) and photothermal therapy (PTT) for colorectal cancer. It also discusses the future prospects and improvement strategies of nanomaterials in precision medicine.

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1 Introduction

According to global epidemiological statistics, colorectal cancer has become one of the most common malignant tumors in the world, with a top three cancer incidence rate and a sharply rising death rate in recent years.[1] Due to its inconspicuous early symptoms and rapid growth and metastasis in the later stages, the cure rate of colorectal cancer, despite some recent improvements, remains in a bottleneck period for developing more treatment methods. Colorectal cancer is typically treated with chemotherapy and targeted therapy after surgery. However, these treatments face challenges such as non-specificity, drug resistance, excessive damage to surrounding tissues, and a high risk of postoperative recurrence and metastasis. In recent years, phototherapy, an emerging tumor treatment method, has demonstrated advantages in protecting surrounding normal tissues, minimizing the impact range, and efficiently activating immune cells. Common methods include PDT and PTT, which kill tumor cells by generating reactive oxygen species (ROS), regulating vascular endothelial growth factor (VEGF), or inducing local thermal damage through photothermal conversion.[2] These methods offer unique advantages in terms of low invasiveness and safety. Nanomaterials, as novel medical materials, can promote photothermal conversion, target drug delivery, and assist in imaging in targeted phototherapy.[3] Consequently, this article provides an in-depth exploration of the multifunctional applications of nanomaterials in addressing the limitations associated with photodynamic therapy (PDT) and photothermal therapy (PTT) for colorectal cancer. A comprehensive summary is presented regarding the engineering paradigms of multifunctional nanoplatforms in colorectal cancer therapeutics, with particular emphasis on three fundamental functionalities: optimization of therapeutic agent delivery systems, enhancement of photophysical energy conversion efficiency, and real-time imaging-guided therapeutic modulation. These groundbreaking advancements in nanomaterial science have unveiled significant potential for precision medicine approaches in colorectal cancer management.

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2 PDT and PTT: complementary mechanisms with distinct challenges

Photodynamic therapy (PDT) and photothermal therapy (PTT) represent two mechanistically distinct phototherapeutic modalities for colorectal cancer management. PDT operates

through photosensitizer-mediated generation of reactive oxygen species (ROS),[4] eliciting therapeutic effects *via* induction of oxidative stress and immunogenic cell death (ICD). The photoactivation mechanism provides exquisite spatial control, facilitating both ROS-mediated irreversible damage to intracellular DNA and subcellular structures to induce ICD, and damage-associated molecular pattern (DAMP)-dependent recruitment of antigen-presenting cells (APCs) to stimulate antitumor immunity.[5] However, the therapeutic efficacy of PDT is frequently constrained by tumor hypoxia microenvironment and off-target photosensitizer distribution. In contrast, PTT employs photothermal conversion to generate localized hyperthermia, enabling direct tumor ablation while enhancing drug permeability. Nonetheless, PTT implementation is challenged by the requirements for precise thermal regulation and heat shock protein (HSP)-mediated thermoresistance.[6–8] These intrinsic limitations underscore the imperative for developing sophisticated engineering solutions to optimize their therapeutic potential. The strategic integration of PDT and PTT through nanotechnology platforms represents a transformative approach to overcome individual limitations and synergistically amplify therapeutic outcomes.[9,10] Nanomaterials facilitate precise spatiotemporal control of photophysical energy conversion, as demonstrated by copper ion nanosheets that concurrently disrupt mitochondrial dynamics and suppress HSP expression. State-of-the-art nanoplatforms, exemplified by Y16-Pr-PEG NPs, achieve remarkable photothermal conversion efficiency (PCE) of 82.4% and singlet oxygen quantum yield of 8.3% within the near-infrared II (NIR-II) window, coupled with enhanced tissue penetration depth.[11] Additionally, pH-responsive [PHC]PP@HA nanocomposites significantly potentiate therapeutic efficacy in hypoxic tumor environments through synergistic PDT/PTT interactions.[12–15] These engineered systems not only address fundamental challenges associated with standalone PDT and PTT modalities but also establish a novel paradigm for precision phototherapy in colorectal cancer treatment.

3 The diversity of nanomaterials in PDT and PTT therapies

3.1 Characteristics of the nanoparticle system

Nanomaterials naturally exist in nature and exhibit diverse morphologies, including nanoparticles, nanorods, nanocages, nanoclusters, and nanofilms.[16] In PDT and PTT applications, material selection depends on function: nanoparticle photosensitizers and photothermal agents improve photothermal conversion efficiency, whereas nanocarriers facilitate drug delivery and biological imaging. Different nanomaterials possess distinct characteristics; the advantages and disadvantages of common nanosystems are discussed below, and their applications are summarized in Table 1.[17]

3.1.1 Matal-based systems. Metal nanomaterials exhibit surface plasmon resonance (SPR), creating strong interactions between incident light and surface electrons that confine light to the nanoscale and enhance energy transfer. This phenomenon not only improves light absorption but also promotes nanoparticle penetration and retention in tumor cells, amplifying therapeutic effects.[18,19] Gold (Au) and silver (Ag) nanoparticles are particularly valuable in PDT and PTT due to their distinctive optical characteristics. Gold nanoparticles readily form gold–thiol bonds,[20] enabling surface functionalization with biomolecules or polymers. Their flexible size range (1–100 nm) and excellent ductility make metallic nanosystems highly suitable for tailored applications. Virus-like gold nanoparticles (AuNV-MTO) exemplify this versatility, mimicking natural viral structures while leveraging gold–sulfur bonds and electronic properties to generate cytotoxic ROS under specific conditions. Their densely packed spike structures intensify plasmon resonance, boosting PTT efficacy.[21] These nanoparticles also interfere with viral infections by binding surface proteins electrostatically, blocking host cell receptor interactions.[22] Through surface modifications and protein assembly alterations, AuNV-MTO triggers potent antitumor immune responses. In CRC MC38 models, *in vitro* assays (live/dead staining, CCK-8) confirmed suppressed proliferation, while *in vivo* studies revealed enhanced fluorescence intensity, indicating superior tissue penetration. The synergistic combination of viral morphology and metallic properties endowed AuNV-MTO with striking antitumor effects, advancing colorectal cancer research.[23,24]

3.1.2 Carbon-based systems. Carbon nanotubes (CNTs)—comprising single-walled (SWCNT) or multi-walled (MWCNT) graphene sheets rolled into cylinders—derive exceptional electrical/thermal conductivity from sp^2-hybridized π-electron clouds, while their mechanical strength stems from robust carbon–carbon σ-bonds and π–π interactions.[25,26] SWCNTs surpass steel in tensile strength, and MWCNTs benefit from interlayer van der Waals forces and covalent carbon bonds.[27,28] Compared with other materials, CNTs exhibit superior stability and deep tissue penetration capability, rendering them uniquely advantageous for bioimaging applications. However, safety concerns persist regarding their potential off-target toxicity accumulation.

3.1.3 Polymer systems. Polymers are high-molecular-weight compounds formed by the covalent linkage of numerous low-molecular-weight monomers. Among them, polydopamine (PDA), a natural melanin-like polymer, is widely utilized in nanoparticle systems. PDA can be synthesized *via* the self-polymerization of dopamine under weakly alkaline conditions. Its molecular structure contains abundant reactive groups, such as catechol and amino groups, enabling the formation of uniform coatings on virtually any material surface through covalent bonding, hydrogen bonding, and π–π stacking interactions, without the need for complex pretreatment.[29] This "universal adhesive" property represents its most notable advantage. Polymer-based carriers, such as poly (lactic-*co*-glycolic acid) (PLGA), allow precise modulation of drug release kinetics by adjusting molecular weight and crosslinking density. Combined with surface-targeting modifications, these carriers facilitate tumor-specific accumulation, thereby enhancing localized therapeutic efficacy.[30] Hydrogel systems rely on highly hydrated polymer networks to mimic the

Table 1 Characteristics and applications of common nanomaterials in cancer therapy

Type of material	Structure	Peculiarity	Apply	References
Liposomes	Contains a phospholipid bilayer structure containing water-soluble drugs	Amphiphilic structure: internal hydrophilic and external lipophilic, so that liposomes can form stable micelles *in vivo* Good biocompatibility and degradability	Improve the delivery efficiency of water-soluble drugs	59
Polymer	Polylactic acid (PLA), polyethylene glycol (PEG)	Regulates the rate of drug release by adjusting the molecular weight and cross-linking of polymers Surface modification functionalization enables targeted delivery	Targeted delivery of drugs to enhance local efficacy	60
Hydrogel	A highly hydrated polymer network that absorbs water and expands	High hydration, mimicking biological environment The rate of drug release is regulated by the degree of cross-linking of the polymer chains	Topical drug delivery Control the rate at which the drug is released into tumor tissues	31 and 61
Metal	Gold, silver, copper, tungsten	Surface plasmon resonance (SPR) effect: enhances light-matter interactions Local surface plasma enhancement effect: increasing singlet oxygen production in PDT	Photosensitizer photothermal agent carrier: the SPR effect enhances light absorption Bioimaging: using nanoparticles to enhance imaging signals	62
Silicon-based	Silicon nanotubes, silicon quantum dots	Good absorption and emission properties in the near infrared region Surface functional: easy to modify, improve biocompatibility and targeting	Targeted drug delivery Bioimaging: as a fluorescent probe to aid tumor imaging	
Magnetism	Iron oxide nanoparticles (Fe_3O_4) or cobalt-based materials as the primary components	Magnetic control: the magnetic field directs the nanoparticles to the tumor area High photothermal conversion efficiency	Precise targeted delivery: nanoparticles are directed to the tumor area using an external magnetic field Bioimaging: used for MRI imaging, auxiliary tumor detection	35
Carbon nano	Graphene, carbon nanotubes (CNTs), and carbon quantum dots (CQDs)	Ultra-high surface area: provides more reaction sites and drug loading capacity	Graphene enhances the light absorption of PDT photosensitizers Bioimaging: enhancing tumor imaging with the fluorescence properties of graphene	28

biological microenvironment. By controlling crosslinking density, the permeation rate of drugs into tumor tissues can be regulated. The *in situ* injection of hydrogels forms a drug reservoir, providing a sustained-release platform for the local treatment of colorectal cancer.[31] Liposomes encapsulate hydrophilic drugs within their phospholipid bilayers. Their amphiphilic structure (hydrophilic interior and hydrophobic exterior) enables the formation of stable micelles *in vivo*, significantly improving drug delivery efficiency while reducing systemic toxicity. This makes liposomes an ideal carrier for photosensitizers.[32,33]

3.1.4 Hybrid systems. Currently, hybrid systems most commonly comprise combinations of organic and inorganic materials. These systems overcome the limitations of single-component materials by synergistically amplifying the advantages of materials with distinct properties, thereby achieving precisely tunable optical characteristics.[34,35] For instance, while polymer aggregation tends to reduce light absorption efficiency, the incorporation of silver (Ag) can enhance light conversion efficiency by leveraging its metallic properties.[30] Capitalizing on these traits, Xie *et al.* developed TiO_2-coated MWCNTs that exploit the nanotubes' electronic states and surface area to provide catalytic sites. At safe NIR concentrations (0–200 μg mL^{-1}), these hybrids downregulated CRC-associated mRNAs (CCNA1, CCND1) and inhibited PI3K-AKT signaling.[36] This nanohybrid approach preserves carbon materials' optical properties while addressing biocompatibility constraints. The TiO_2-MWCNT system exhibits unprecedented photostability and catalytic activity, overcoming traditional organic nanomaterial limitations like photobleaching and

reaction instability.[37] However, the synthesis of hybrid systems is more complex, and many non-eco-friendly materials involved may pose environmental risks.

3.2 Critical performance balancing and conversion bottlenecks

3.2.1 Efficiency-security trade-off. Metal-based systems exhibit excellent photothermal conversion efficiency; however, they carry the risk of ion leakage, which may induce oxidative stress and lysosomal damage.[38] High-valent metal ions can be cytotoxic.[39] In one study, the ligand field effect of epigallocatechin-3-gallate (EGCG) effectively reduced high-valent metal ions to less toxic low-valent states while maintaining catalytic cycling, thereby minimizing the toxicity of free high-valent metal ions. Additionally, surface-modified hyaluronic acid (HA), an endogenous glycosaminoglycan, not only reduced nonspecific adsorption of the material to normal cells but also enhanced its accumulation at tumor sites, mitigating damage to healthy tissues. Under 650 nm laser irradiation, this nanomaterial achieved high efficiency through mild photothermal effects, avoiding the thermal damage to surrounding healthy tissues typically associated with conventional high-intensity photothermal therapy.[40] Furthermore, by suppressing heat shock proteins, it enhanced the sensitivity of catalytic therapy, ensuring both therapeutic efficacy and safety.

In the optimization of materials, one study revealed that the amorphous-crystalline composite-structured copper–silver sulfide nanomaterial (Cu_xS–Ag_2S) exhibits significantly enhanced photothermal conversion efficiency through non-radiative relaxation, attributed to the presence of dangling chemical bonds and atomic interstices in the amorphous phase. This structure substantially reduces electron–hole recombination probability, thereby markedly increasing the quantity of charge carriers participating in reactions.[41] The temperature gradient-driven directional charge migration generates electric current or potential, and this efficient carrier separation enables more charges to engage in enzymatic catalytic cycles or thermoelectric reactions, further amplifying therapeutic efficacy. Another study considered that zinc and copper, as essential trace elements in humans, possess safer metabolic pathways compared to highly toxic heavy metals, thereby reducing the risk of long-term residual toxicity.[42] These nanoparticles are designed to decompose selectively within the tumor microenvironment, releasing metal ions and active substances, while maintaining high stability in normal tissues to minimize damage to healthy cells. This mechanism achieves a "targeted activation" feature with low toxicity.[43]

The toxicity of carbon-based systems is influenced by their size and surface charge. The size determines the direct interaction mode between carbon-based materials and biomolecules, while the delivery of nanomedicines relies on their surface charge distribution and hydrophobicity. Experimental evidence indicates that positively charged carbon-based systems may exhibit stronger toxicity, whereas negatively charged systems demonstrate slower metabolic rates.[44] Jiang *et al.* investigated seven different carbon-based materials and found that structural variations significantly alter toxicity mechanisms. Within the same category of carbon-based nanomaterials, smaller particles exhibited markedly higher toxicity than larger ones, likely due to their greater specific surface area.[45]

Polymers are widely employed as nanocarriers in medicine. However, small-molecule byproducts released during polymer degradation may accumulate to cytotoxic or pro-inflammatory concentrations. Wu *et al.* conducted animal experiments to evaluate the safety of polymer-derived nanoplastics. Their findings demonstrated that chronic exposure to nanoplastics reduced both the abundance of *Akkermansia muciniphila* and the expression of tryptophan metabolite indole-3-lactic acid (ILA), indicating chronic toxic effects.[46] Studies suggest that active transport reduces damage to healthy tissues, yet its poor circulatory stability makes localized administration preferable for minimizing dosage and toxicity.[47] Additionally, additives and processing agents incorporated to enhance performance may introduce toxicity and environmental concerns.[48] Consequently, leveraging the biocompatibility of polymers in combination with complementary materials has gained broader clinical acceptance. Given the diversity of polymers, determining their toxicity thresholds and properties is critical.[49]

Conventional nanoparticle synthesis often relies on physicochemical methods involving environmentally hazardous reagents.[43] To address this, researchers have explored eco-friendly alternatives. Recently, Song *et al.* developed a semi-sustainable approach using genetically modified bacteria to synthesize silver nanoparticles (AgNPs), which exhibit high photothermal conversion efficiency and dual therapeutic-imaging potential.[50] Another team employed Thalictrum foliolosum leaf extract as a bio-reducing and stabilizing agent for AgNPs synthesis, entirely avoiding toxic chemicals. This method aligns with green nanotechnology principles—being clean, cost-effective, and safe—while overcoming the functional limitations of chemically or microbially synthesized AgNPs.[51] The resulting particles demonstrated negligible toxicity and multifunctional biomedical potential, including antifungal, antioxidant, and anticancer properties, enabling versatile biomedical applications. Furthermore, these AgNPs show promise as biosensors.[52,53] Current studies highlight their potent cytotoxicity against squamous cell carcinoma and melanoma cell lines, suggesting future applicability in broader oncological therapies.[52]

3.2.2 Clinical suitability of route of administration. In PDT and PTT, intravenous, topical, and oral administration remain the predominant routes of drug delivery. However, their therapeutic efficacy is limited by the rapid clearance of nanoparticles by the mononuclear phagocyte system during systemic circulation and their propensity for hepatic accumulation, which may induce toxicity. Consequently, alternative approaches such as intratumoral and intra-arterial injections have garnered extensive research attention.[54,55] Jiang *et al.* developed a core–shell nanosphere-based photodynamic integrated nanomotor (PS@PDA) that employs peritumoral subcutaneous injection. This system reduces the risks associated with photothermal agent delivery while achieving multiple therapeutic objectives:

the photothermal effect not only provides propulsion but also induces thermal ablation of subcutaneous tissue. With NIR-II real-time imaging guidance, the nanomotor demonstrates autonomous propulsion through subcutaneous tissue with precise tumor targeting. The system is scalable, can be adjusted by replacing polystyrene cores, is highly biocompatible, and is easy to manufacture. Experimental validation confirmed significantly enhanced tumor accumulation rates and reduced off-target toxicity.[56] Although challenges remain regarding deep tumor penetration and integration with commercial systems, this approach establishes a novel minimally invasive paradigm for precise treatment of superficial lesions such as colorectal cancer metastases in the abdominal wall. While intratumoral injection improves local drug accumulation, its applicability is restricted to superficial or palpable lesions. Therefore, further research is warranted to optimize administration routes and identify the most suitable delivery strategies for specific clinical scenarios.

3.2.3 Clinical translation challenges. In clinical translation, the application of nanoparticles (NPs) for colorectal cancer (CRC) remains predominantly in the experimental stage due to the unique gastrointestinal environment. Significant variations in intestinal circulation time, distribution, metabolism, and excretion (collectively termed ADME) result in highly complex pharmacokinetics, compounded by the lack of real-time monitoring methods. Further bottlenecks in nanomaterial development include intricate fabrication processes and prohibitive costs (Table 2). Among nanomaterials, liposomes—with their high biocompatibility—were the first to achieve clinical adoption. A recent Phase I trial (NCT04784767) employed a hybrid nanoparticle system comprising SARS-CoV-2 spike protein (S protein)-ferritin subunits linked by peptide connectors and encapsulated in unilamellar liposomes to develop a pan-β-coronavirus vaccine.[57] This design leverages adjuvant encapsulation to reduce nonspecific accumulation while enhancing biosafety. Another Phase II trial utilized albumin-bound paclitaxel nanoparticles (nab-paclitaxel), an FDA-approved nanomaterial since 2005. The natural albumin carrier minimizes immunogenic reactions, potentiates paclitaxel cytotoxicity, and indirectly improves tumor-targeting efficiency.[58] Nevertheless, translating nanomedicines for CRC from bench to bedside faces unresolved challenges, demanding intensified exploration. Key priorities include: (1) developing smart nanocarriers responsive to tumor microenvironment cues for precision targeting; (2) identifying personalized biomarkers to overcome tumor heterogeneity and mitigate immune responses; (3) establishment of more sophisticated *in vivo* dynamic monitoring models coupled with toxicity assessment models; (4) innovating scalable production methods with cost-effective controls.

4 Tumor microenvironment in colorectal cancer: immune evasion and metabolic dysregulation

Colorectal cancer (CRC), a therapeutically challenging malignancy, is characterized by a multifaceted tumor microenvironment (TME) shaped by intestinal anatomical specificity and metabolic peculiarities[63] (Fig. 1). This complexity manifests through four interconnected pathological axes: (1) an immunosuppressive milieu orchestrated by inhibitory cytokines (*e.g.*, TGF-β, IL-10) and suppressive immune infiltrates (Tregs, M2-polarized macrophages); (2) chronic inflammation-driven tumor progression *via* pro-inflammatory mediators (*e.g.*, IL-6, TNF-α) that potentiate immune evasion and metastatic propensity;[64,65] (3) microbiota dysbiosis (*Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis* (ETBF), *Enterococcus faecalis*) contributing to epithelial barrier dysfunction;[66–68] (4) a distinctive redox disequilibrium featuring hypoxia, acidic pH, and aberrant levels of endogenous hydrogen sulfide (H_2S, 0.3–

Table 2 Nanomedicine in recent cancer clinical trials

Material category	NCT number	Phase	Clinical medication	Route of administration	Conditions	Experimental status
Liposomes	NCT07047560	2	Liposomal irinotecan(II) administered in divided doses in combination + 5-FU/LV and bevacizumab	Intravenous infusion	Colorectal cancer	Recruiting
	NCT07044921	2	Irinotecan liposomes(II) + cetuximab bevacizumab	Intravenous infusion	Drug-resistant colorectal cancer	Recruiting
	NCT07050394	1	HNF4α srRNA	Intravenous infusion	Colorectal cancer	Recruiting
Carbon	NCT06048367	1	CNSI-Fe(II)	Intratumoral injection	Solid tumors	Completed
Polymer	NCT06752811	3	Paclitaxel polymer micelles + gemcitabine hydrochloride	Intravenous infusion	Metastatic pancreatic cancer	Recruiting
	NCT05048082	2	Pegsitacianine	Intravenous infusion	Malignant tumors of the lungs	Completed
	NCT06706895	2	Paclitaxel polymer micellar + fruquintinib capsules	Intravenous infusion	Advanced gastric cancer	Not yet recruiting
	NCT06039202	2	CA102N + trafluridine/ tepyrimidine (TAS-102)	Intravenous infusion	Metastatic colorectal cancer	Recruiting
Metal	NCT05685602	2	NU-0129	Intravenous infusion	Glioblastoma	Completed

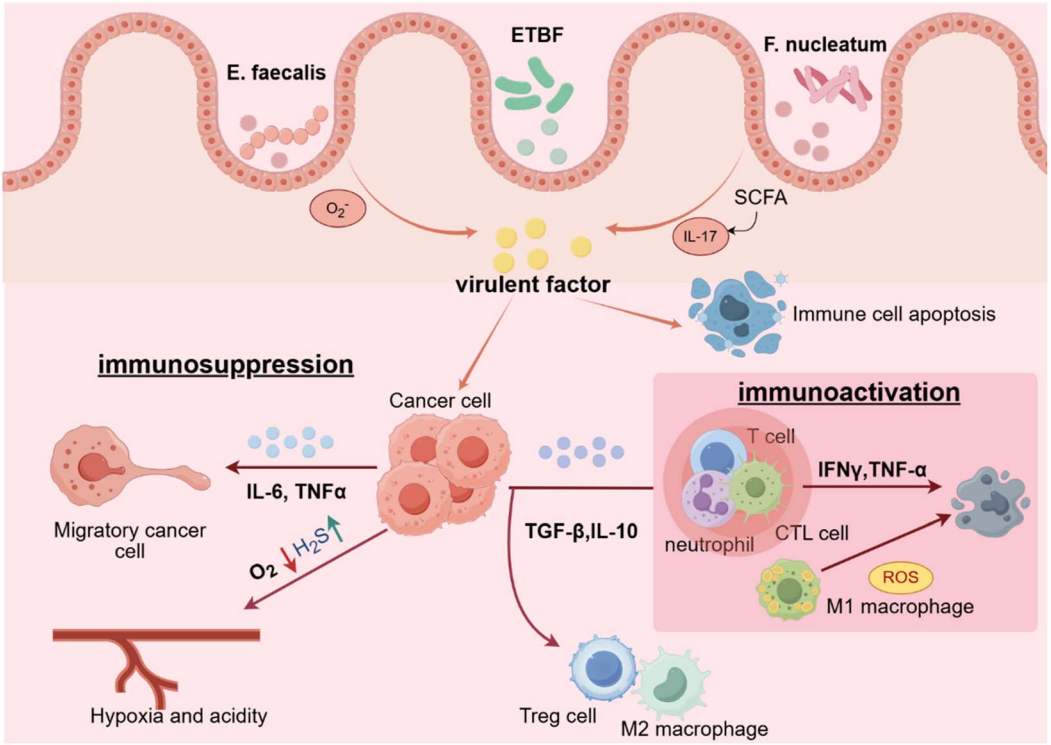

Fig. 1 Tumor microenvironment features of high heterogeneity in CRC pathogenic microbiota, including *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis* (ETBF), and *Enterococcus faecalis*, orchestrate TME dysregulation through a tripartite mechanistic axis: (1) microbial-derived oncotoxins instigate genomic instability and potentiate oncogenic signaling cascades; (2) concomitant TGF-β/IL-10-mediated immunosuppression and IL-6/TNF-α-driven pro-inflammatory signaling foster immune polarization imbalance; (3) profound metabolic reprogramming manifesting as acidic hypoxia and dysregulated H_2S/H_2O_2 redox homeostasis. The figure was created by Figdraw (https://www.figdraw.com).

3.4 mM) coupled with dysregulated ROS, glutathione homeostasis.[69,70]

Neoplastic cells exhibit metabolic plasticity by utilizing H_2S for bioenergetics while deploying antioxidant defenses to mitigate oxidative catastrophe. The biphasic role of H_2S—activating pro-tumorigenic signaling at subtoxic concentrations while inducing oxidative lethality at higher thresholds—compels tumor cells to maintain precise redox disequilibrium. This pathophysiological paradox presents a unique therapeutic vulnerability. Capitalizing on this, a sophisticated H_2S-activated theranostic platform was engineered: hyaluronic acid (HA)-encapsulated TPZ@$Cu_2Cl(OH)_3$-HA (TCuH) nanoparticles (NPs). This system orchestrates multidimensional TME modulation through synergistic integration of cuproptosis and PTT. Under NIR-II photoirradiation in H_2S-rich TME-mimicking conditions, TCuH NPs undergo sulfidation with NaHS to yield photothermal Cu_9S_8 nanocrystals, concomitant with controlled release of the hypoxia-activated prodrug tirapazamine (TPZ). *In vitro* analyses revealed that laser-activated TCuH NPs potentiate sulfidation cascades and Fenton-like reactions under dual hypoxia/H_2S stress, achieving remarkable apoptosis induction (96.5%) that eclipses conventional monotherapies.[71,72] These findings underscore the therapeutic supremacy of combining chemodynamic therapy (CDT), cuproptosis, PTT, and hypoxia-activated chemotherapy. The TCuH platform exemplifies how nanotechnology can harness CRC's pathophysiological complexity to develop innovative theranostic strategies, establishing a blueprint for precision targeting of multifactorial TME.

5 Multidimensional applications of nanomaterial-driven photodynamic and photothermal therapy in colorectal cancer

Nanoparticles exhibit extensive applications in PDT and PTT, primarily encompassing the following aspects: serving as highly efficient photosensitizers and photothermal agents to enhance therapeutic efficacy, functioning as drug carriers to achieve targeted delivery, utilizing optical properties to facilitate precise lesion localization through bioimaging, and enabling highly sensitive detection of tumor biomarkers in liquid biopsy (Fig. 2). These capabilities provide crucial support for the synergistic application and therapeutic optimization of PDT and PTT. The specific details are presented below.

5.1 Photosensitizers and photothermal agents

High-performance photosensitizers and photothermal agents typically feature efficient light absorption, a robust ability to generate reactive oxygen species (ROS), and strong photothermal conversion efficiency.[73] Moreover, their *in vivo*

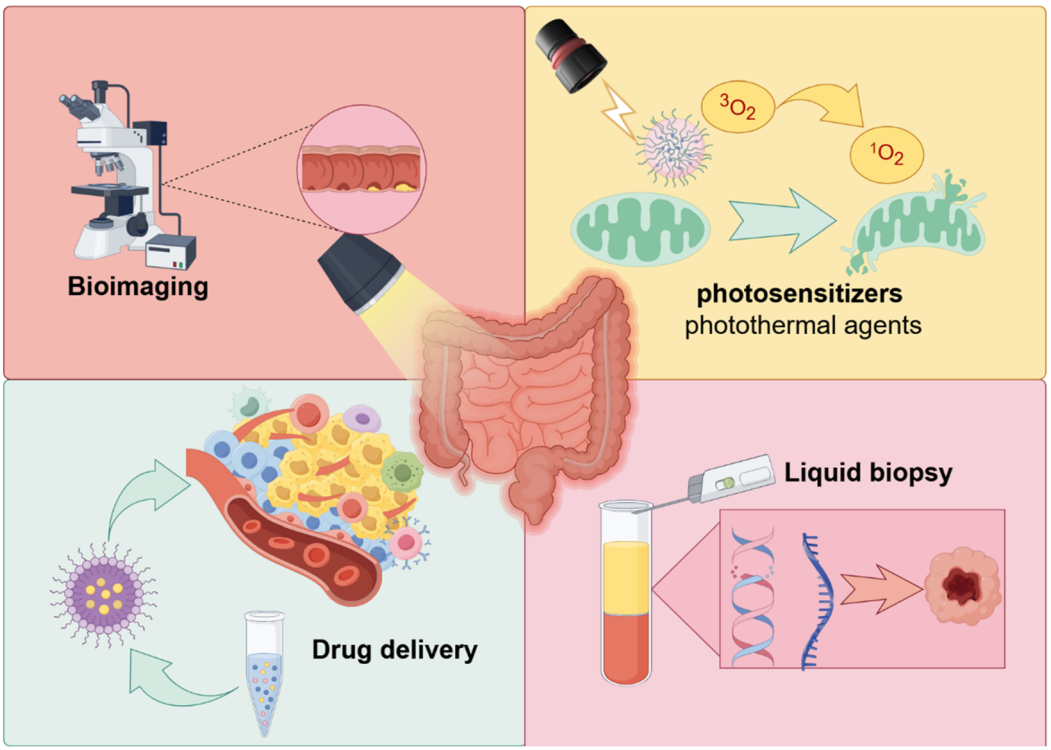

Fig. 2 Application of nanoparticles in PDT and PTT for colorectal cancer treatment: (1) carbon-based nanomaterials and quantum dots possess unique optical properties that enable precise spectral emission by tuning their size, allowing for multi-channel and multi-color imaging signals. (2) Metal nanoparticles, in particular, can generate intense surface plasmon resonance effects. As photosensitizers and photothermal agents, they exhibit high photothermal conversion efficiency. (3) The biocompatibility and tunability of nanoparticles highlight the advantages of surface modification and functionalization, enabling targeted drug delivery mechanisms that enhance drug stability and precision. (4) As sensing platforms, nanoparticles can amplify weak biological signals through their electronic conductivity and luminescence properties, thereby improving the sensitivity of liquid biopsy. The figure was created by Figdraw (https://www.figdraw.com).

residence time, safety, and biocompatibility are also vital attributes. The incorporation of nanoparticles enhances the excitation and heat conversion efficiency through surface plasmon resonance (SPR) effects and the high specific surface area, while benefiting from their material properties, which allow for safe *in vivo* degradation. Fe_xMo_yS-PEG, a dual-metal nanoparticle carrier modified with polyethylene glycol (PEG), demonstrates superior ROS generation and glutathione (GSH) depletion. In CRC therapy, these nanoparticles exhibit a photothermal conversion efficiency as high as 67.14% and significantly inhibit CRC by altering tumor cell metabolism.[62] Experimental results confirm that Fe_xMo_yS-PEG nanoparticles exhibit negligible toxicity, further underscoring their therapeutic potential in CRC treatment.[74] In a combined PTT and chemotherapy approach, SN38-conjugated hyaluronic acid (HA)-gold nanoparticles (SN38-HA AuNP) leverage the high photothermal conversion properties of inorganic materials while enabling targeted drug delivery upon red LED irradiation.[75] This study has successfully established a highly efficient targeting strategy for colorectal cancer metastases. AuNPs, by virtue of their exceptional photothermal conversion efficiency, not only significantly potentiated tumor cell membrane permeability but also facilitated spatiotemporally controlled release of the chemotherapeutic payload SN38. The engineered HA coating conferred dual functionality: enhanced metastatic site accumulation through CD44 receptor-mediated active targeting,[76] and improved biocompatibility with reduced off-target effects on normal tissues. This multifunctional nanoplatform represents a therapeutically safe and precisely controllable paradigm, demonstrating significant potential for clinical translation.

5.2 Drug delivery

Nanomaterials are increasingly utilized for drug-targeted delivery to tumor-enriched regions, where they activate and amplify immune responses. These materials can incorporate drug molecules into their structure *via* non-covalent physical interactions and release them in a controlled manner within specific environments. Alternatively, they form stable drug-carrier complexes by covalently bonding with the drug molecules. Drug delivery systems can be categorized into active and passive targeting strategies, depending on the targeting mechanism. Nanomaterials, owing to their large surface-area-to-volume ratio and potent targeting capabilities, can efficiently and safely deliver drugs to tumor sites.[77] Furthermore, their exceptional biocompatibility facilitates cell adhesion, proliferation, and differentiation, while minimizing immune reactions and ensuring safe *in vivo* degradation.[78]

Active targeting drug delivery is achieved by modifying the surface of nanoparticles with specific ligands, enabling them to bind selectively to target receptors or biomarkers, thereby

ensuring precise drug delivery.[79] Additionally, novel approaches have been implemented, including the utilization of tumor microenvironment-specific stimuli, external field-mediated enrichment of nanocarriers, and biomimetic material-based active targeting. This strategy significantly enhances drug delivery efficiency and accuracy, offering high selectivity and enabling direct drug targeting to specific cells or tissues, thus improving therapeutic safety. To address challenges related to the oral absorption of drugs, recent studies have developed innovative combinatory PLGA nanoparticles by conjugating the chemotherapeutic agent 5-fluorouracil (5-FU) with the natural flavonoid quercetin (QC), resulting in improved drug targeting.[80] These combinatory nanoparticles effectively inhibit colorectal cancer cell growth, demonstrating promising potential for CRC chemotherapy. Moreover, leveraging cancer's metabolic reprogramming characteristics, Yang *et al.* designed an active targeting delivery system—MPB-3BP@CM NPs—to inhibit CRC glycolysis. Incorporating cell membrane engineering, they developed biomimetic nanoparticles. This platform not only enables precise delivery of the glycolysis inhibitor 3-bromopyruvate (3BP) but also confers "stealth" capability and targeting specificity to the nanocarriers by mimicking natural cell membranes *in vivo*, thereby minimizing adverse effects. In both *in vitro* and *in vivo* studies using the HCT116 colorectal cancer model, 3BP induces apoptosis in tumor cells by disrupting glycolysis-induced starvation and reducing lactate production, thus enhancing the tumor microenvironment.[81] In a recent study, Lin *et al.* similarly employed a biomimetic extracellular vesicle (EV)-encapsulated nanomaterial technology. Gene set enrichment analysis (GSEA) revealed significant increases in B cells and T cells, accompanied by enhanced mitochondrial oxidative phosphorylation in T cells. This approach effectively alleviated T cell exhaustion and restored their metabolic adaptability. Experimental results demonstrated that this system exhibited negligible toxicity even at high concentrations up to 1000 μg mL^{-1}. The combination of such biomimetic materials with immunostimulation provides novel insights for overcoming the hostile tumor microenvironment and achieving durable immunity.[82,83]

Passive targeting, an alternative approach, relies on the enhanced permeability and retention (EPR) effect. The high permeability of blood vessels and impaired lymphatic drainage in the tumor microenvironment lead to higher nanoparticle concentrations within tumors compared to normal tissues.[43] However, despite the general effectiveness of the EPR effect across many tumor types, its permeability varies between different tumors. Thus, improving passive targeting efficiency remains a significant challenge. To overcome these limitations, researchers have designed multifunctional nanoparticles that combine various targeting strategies and optimize drug release properties to enhance drug accumulation in tumor regions and improve therapeutic outcomes.[43,84]

5.3 Bioimaging

Bioimaging technology effectively monitors the distribution of photosensitizers or photothermal agents, evaluates tumor cell response to treatment, and assesses post-treatment effects. It is commonly used for early cancer diagnosis.[85] Techniques like fluorescence imaging or photoacoustic imaging allow real-time evaluation of the efficacy of PDT and PTT, enabling the determination of optimal illumination time, intensity, and heat to enhance treatment precision. The introduction of nanomaterials improves sensitivity to cancer biomarkers in bioimaging. Surface modifications facilitate targeted dynamic monitoring of specific tumor markers. Additionally, the biological properties of nanomaterials enable dynamic monitoring and multimodal imaging during treatment.[86] Furthermore, the excellent optical properties of metal nanomaterials significantly enhance the imaging contrast between tumors and surrounding normal tissues.

Magnetic resonance imaging (MRI) utilizes a strong magnetic field and radio waves to generate detailed images of internal tissues non-invasively.[35] Contrast agents improve the resolution and clarity of these images. Traditional MRI contrast agents, such as gadolinium (Gd)-based agents, have certain toxic effects and are easily cleared from the body,[87] limiting their use to imaging soft tissues and structures. Nanomaterials, widely studied as safer and more effective alternatives, exhibit strong magnetism and can generate intense magnetic responses in a magnetic field, significantly enhancing image contrast and improving lesion visibility.

Fluorescence imaging is commonly used for tracking and monitoring tumor markers. There is a need for materials with stable and sensitive fluorescence properties, high emission intensity, and the ability to monitor biological activities reliably.[88] Mishra *et al.* developed a novel material, CQD/Ag, through an environmentally friendly method by combining silver heterostructures with carbon quantum dots (CQDs). This material was evaluated for its anticancer activity and potential as an imaging agent in colorectal cancer (HCT 116) cell lines. The core of CQDs consists of amorphous or partially graphitized carbon with varying degrees of sp^2 hybridization. Due to the quantum confinement effect, the movement of electrons in CQDs is quantized, giving rise to significant fluorescence properties even at small sizes. Studies have found that CQD/Ag can not only downregulate the Akt-BCL2 axis to promote cancer cell death, but its good photostability and high fluorescence intensity also demonstrate its potential as a bioimaging agent.[27] To overcome the limitations of traditional CRC fluorescence imaging, such as low signal-to-noise ratio, nonspecific probe distribution, and static monitoring, a study designed an intravenous and sprayable fluorescent nanoprobe called Poly-g-BAT. This probe utilizes gamma-glutamyl transpeptidase (GGT), which is rapidly internalized by tumors, to rapidly absorb the fluorescent probe and undergo a quinone reduction reaction with other enzymes in the body, releasing a fluorescent signal. Experimental results showed that Poly-g-BAT could detect very small colorectal tumors (less than 1 mm in diameter), achieve a high tumor-to-normal ratio (TNR) of up to 12.3, and display clear tumor boundaries within three minutes of *in situ* spraying.[89] These findings demonstrate the high sensitivity and rapid, precise imaging capabilities of Poly-g-BAT, enabling real-time, precise tumor localization during surgery and early

diagnosis for timely intervention. This technology has significant potential in image-guided tumor resection for colorectal cancer.

5.4 Liquid biopsy

Imaging technology provides spatial and structural guidance for PDT/PTT, while liquid biopsy provides molecular-level information on tumor dynamics, enabling more comprehensive treatment planning and monitoring. Liquid biopsy, as a non-invasive diagnostic tool, utilizes biomarkers present in bodily fluids like blood and urine to provide early tumor detection, prognosis evaluation, and treatment response monitoring. It has found adequate application in the early diagnosis of CRC. Nanomaterials, with their efficient biocompatibility, are often used as carriers to bind with specific biomarkers, significantly improving the capture efficiency of target molecules.[90] Additionally, they can be utilized in the development of novel sensors and detection platforms, enabling real-time monitoring of CRC markers at low concentrations and helping to assess tumor invasiveness and metastasis risk. As highly effective sensors, nanomaterials exhibit signal amplification properties. When bound to target molecules, they can enhance signal detection through their excellent electron conduction and luminescence characteristics. However, single biomarker detection often suffers from low specificity and limited information. Given the close relationship between high hydrogen sulfide levels and the tumor microenvironment of colorectal cancer, a study combined hydrogen sulfide with miRNA-211 to construct a 3D DNA ordered network for the detection of dual markers. This sensor, embedded with silver nanoparticles, generates quantum dots through the corrosion of nanoparticles by hydrogen sulfide. Experimental evaluation successfully demonstrated stable and precise tumor imaging using HCT 116 cells.[91] Carcinoembryonic antigen (CEA), a biomarker significantly elevated in CRC patients, was targeted for high-sensitivity real-time monitoring. An electrode array (MX@CNT) consisting of $Ti_3C_2T_x$ MXene combined with carbon nanotubes (CNT) was successfully prepared using template-assisted filtration technology. As a novel and environmentally friendly electrochemical sensing platform, it operates based on the MB-aElisa mechanism. Through alkaline phosphatase (ALP) catalysis, it hydrolyzes the 1-NPP substrate to generate the electroactive product 1-NP, producing a detectable electrochemical signal. Experimental testing showed that the sensor has a broad linear range for CEA detection (0.005 to 1.0 ng mL^{-1}) and can achieve accurate detection at extremely high sensitivity, holding promise for contributing to the early diagnosis of colorectal cancer.[92]

6 Combination therapies: a novel strategy to enhance colorectal cancer treatment efficacy

The combination therapy better highlights the therapeutic advantages and synergistic effects of photodynamic therapy PDT and PTT in colorectal cancer. This synergistic interaction not only enhances tumor cell cytotoxicity but also effectively reduces the risk of drug resistance that may arise from monotherapy (Table 3). Moreover, the combined treatment can activate systemic antitumor immunity and exert inhibitory effects on non-illuminated metastatic lesions. This represents a breakthrough in controlling distant metastases in advanced colorectal cancer. Below are several common combination strategies.

6.1 Ferroptosis

Ferroptosis, a regulatory mechanism induced by excessive iron accumulation within cells, leads to glutathione depletion and cell membrane damage through lipid peroxidation, ultimately resulting in cell death. In tumor therapy, ferroptosis is often combined with other immunotherapies to induce specific antitumor effects due to limited intracellular iron levels and immune evasion mechanisms in tumor cells.[93] Breaking the limitations of a single cell death mechanism, the "crosstalk" between two distinct death modalities enables tighter coupling of cellular cytotoxicity with immune activation. The release of iron ions *via* exogenous nanoparticles and endogenous photothermal-induced ferritin degradation mechanisms can significantly enhance the response rate of immunotherapy in "cold tumors".[94] Recently, Du *et al.* demonstrated that simultaneous induction of apoptosis and cuproptosis through a unified nanoplatform—utilizing ferroelectric catalysis, inhibition of copper efflux, and immune activation by cellular debris—resulted in complementary cytotoxic effects. This was achieved through the synergistic action of antigens released by apoptosis and metabolic disorders triggered by cuproptosis.[33] This has inspired a study utilizing iron death mechanisms in the development of nanoparticles for CRC treatment. By integrating with PTT, a nanoplatform, GO_x@FeNPs, was designed based on the conversion efficiency of inorganic materials and the Fenton effect of iron ions. In this system, GO_x enzyme catalyzes the accumulation of peroxide with Fe^{2+}, while cyclic arginine glycine aspartic acid (cRGD) peptide and aniline (AA) in the nanoparticles bind to specific integrin receptors and chemical groups on the cell surface, enhancing targeting capability.[95] In controlled experiments, fluorescence signals clearly demonstrated an increase in ROS and lipid peroxidation (LPO) in the experimental group. When combined with PTT, the study found a significant enhancement in cellular ironization and immunogenic cell death (ICD) in the CT26 model.[96] Furthermore, the experiment integrated αPD-L1 immune checkpoint inhibitors, achieving a remarkable 91.13% tumor suppression rate, exhibiting a significant synergistic effect.

6.2 Immunotherapy

Immunotherapy utilizing nanomaterials as functional agents can trigger the ICD process in cancer cells, inducing the uptake of immunogenic tumor antigens by antigen-presenting cells (APCs) and activating them.[97] Nanomaterials can also serve as adjuvants, directly inducing the activation of inflammasomes and stimulating cytokine production to activate the immune system and alleviate immunosuppression. The versatility of

Table 3 Selected studies on the application of nanomaterials in PDT/PTT combined with other therapies for the treatment of CRC in recent years

Combination therapy	Nanoparticles	Treatment	Characteristics	References
Ferroptosis	PCO	PTT	Accelerated Fenton reaction	130
	CKPP	Cuproptosis	Combination of ROS homeostasis dysregulation and glycolysis inhibition leads to cuproptosis	131
	GO_x@FeNPs	PTT, αPD-L1	Accelerates the Fenton reaction and enhances the process of PTT-induced ICD	96
Immunotherapy	P/ICG NPs	E@L-P/ICG, PTT	Enhancement of adaptive immune response by inducing tertiary lymphoid structure (TLS) production using the photosensitized bacterial system of E@L-P/ICG	132
	M@o-A	PDT, chemotherapy	Blocks highly PD-L1-expressing tumor cells, synergistically catabolizing ROS and oxaliplatin (OXA) release	102
	mTHPC@VeC/T-RHD NP	PDT, PD-L1 blocker	Synergistically blocking immunosuppressive signaling pathways and activating anti-tumor immune responses	133
CDT	PZTC/SS/HA NC	PTT, CDT	Simultaneous activation and enhancement of PTT-induced local thermotherapy and disulfide bond-induced GSH depletion	71
	CBS NSs	Sonopiezoelectric therapy (SPT) and CDT	Ultrasound increases Fenton's efficiency and degrades the tumor collagen network	108
X-PDT	Cu-Cy NP	X-PDT	ROS production induced directly by X-rays	111
Metabolic reprogramming	MPB-3BP@CM NPs	Glycolysis inhibitors	Biomimetic nanomedicine platforms inherit the properties of pristine cell membranes to improve survival time *in vivo* HK2 is involved in the inhibition of glycolysis	81
	HA/H780-IVM NPs	Phototherapy, chemotherapy	Coupling IR780 and the autophagy inhibitor hydroxychloroquine HCQ to make a photosensitizer that generates large amounts of ROS under phototherapy	134
	LnNPs	PDT	PDT synergistically inhibits metabolic reprogramming with 2-deoxy-D-glucose (2DG) under near-infrared light excitation	119
Gasotherapy	Cu_2O/BNN6@MSN-Dex	PTT	NO release enhances PTT ablation of tumors and pathogenic bacteria	135

nanomaterials makes them excellent candidates for manually regulating the cancer immunity cycle. PDT and PTT, when used alone, carry risks such as shallow efficacy and easy recurrence.[98,99] Additionally, CRC is prone to metastasis, high heterogeneity, and drug resistance. Combination therapies provide an additional layer of protection for the prognosis of CRC, with immunotherapy being the most common approach. Immune checkpoint inhibitors relieve the inhibition of T cells by blocking the interaction between PD-1/PD-L1 or CTLA-4.[100] To reduce potential adverse reactions associated with intraperitoneal injection, a metal–organic framework (MOF) nanoparticle system, M@O-A, was developed.[101] This system encapsulates the chemotherapy drug oxaliplatin (OXA) and PD-L1 aptamers, aiming to integrate PDT, chemotherapy, and immunotherapy. MOFs, with their high porosity and selectivity in molecular sieving and adsorption processes, serve as photosensitizers capable of stably generating ROS.[102] Under irradiation at a wavelength of 640 nanometers, this nanosystem significantly enhances anti-tumor immune effects and improves safety.

6.3 Chemodynamic therapy (CDT)

Chemodynamic therapy (CDT), a novel minimally invasive treatment, employs nanomaterials for targeted drug delivery. It generates or transforms toxic molecules like hydroxyl radicals ($^{\bullet}OH$)[103,104] through local chemical reactions within cells, causing direct harm to tumor cells. Considering the high hydrogen sulfide and glutathione tumor microenvironment characteristics of CRC,[105] Zeng *et al.* designed a polyoxometalate nanocluster, POM-Co, which self-assembles into larger POM-CoS clusters under the action of H_2S in the tumor microenvironment. This process produces hydroxyl radicals ($^{\bullet}OH$) and singlet oxygen ($^1O_2$) through the Fenton reaction, effectively inhibiting tumor cells. Both *in vitro* and *in vivo* experiments demonstrate the strong photothermal conversion capability and catalytic activity of POM-Co nanoclusters.[106] Particularly in CRC treatment, the POM-Co nanocluster experimental group, under laser irradiation, achieved a tumor site temperature as high as 48 °C, enabling precise treatment. Furthermore, its half-life of 1.63 hours and the biodegradable, recyclable nature of the nanoclusters highlight their excellent safety profile,

providing a novel strategy for the precision treatment of CRC.[107] Based on CDT, a recent study by Yu *et al.* demonstrated that the incorporation of ultrasound significantly accelerates immune activation. The electric field generated by ultrasound not only enhances $^{\cdot}OH$ production to improve Fenton reaction efficiency but also drives Ca^{2+} influx to activate matrix metalloproteinases (MMPs), thereby synchronously degrading the tumor collagen network. Meanwhile, NIR light irradiation induces localized thermal effects that denature and relax dense collagen, reducing tissue stiffness and markedly improving the intratumoral penetration depth of nanoparticles.[108] Such combinatorial strategies integrating CDT with immunotherapy, ferroptosis, and other mechanisms exhibit superior safety profiles and therapeutic efficacy in preclinical studies.

6.4 X-PDT

PDT is often limited to superficial tumors, and commonly used UV, visible, or NIR light-induced PDT suffers from low tissue penetration and rapid energy attenuation. Researchers have explored the integration of X-rays, which have strong penetration power, to develop photosensitizers that can directly absorb X-rays and attach to nanomaterials.[109] This approach enables the photosensitizer to more effectively reach deep tumors and exert a multi-pronged attack on tumor cells through different mechanisms, enhancing the anti-tumor effect.[110] A study employing copper-cysteamine (Cu-Cy) NPs has brought X-PDT out of the laboratory and into clinical research, utilizing a deep-seated model to investigate Cu-Cy nanoparticles. By mimicking clinical conditions with a clinical linear accelerator featuring lower radiation therapy (RT) doses, this approach provides a realistic perspective for cancer treatment.[111]

Hydrogen peroxide can assist tumor cells in breaking through the matrix barrier by activating enzymes such as matrix metalloproteinases (MMPs) that decompose the extracellular matrix. It also promotes tumor angiogenesis and enhances immunosuppressive effects. In response to the hypoxic and high hydrogen peroxide environment of the tumor microenvironment (TME), Zheng *et al.* designed AVPt@HP@M nanoparticles with catalase-like properties based on X-PDT combined with radiotherapy. These nanoparticles aim to improve the hypoxic environment and enhance radiotherapy sensitivity by interfering with purine metabolism. *In vitro* treatment evaluation using HCT-116 colorectal cancer cells showed a significant decrease in cell survival rate to less than 30% at an AVPt@HP@M concentration of 100 μg mL^{-1}. *In vivo* fluorescence imaging demonstrated the excellent targeting ability and good safety profile of AVPt@HP@M, which could be timely excreted from the body. By labeling HIF-1α and the DNA damage marker γ-H2AX with red and green fluorescence, respectively, the study found that the AVPt@HP@M treatment group exhibited the brightest green fluorescence and significantly suppressed red fluorescence.[112] This indicates that AVPt@HP@M can regulate the tumor microenvironment and enhance radiotherapy sensitivity, showcasing its potential as an effective combination therapy strategy.[113–115] However, as a strong penetrating ray, X-ray irradiation requires precise control of the dose to avoid damage to normal tissues while ensuring effective treatment of the tumor area.

6.5 Metabolic reprogramming

Tumor cells have high metabolic demands in a hypoxic environment. A novel tumor treatment strategy induces cell autophagy or apoptosis by restricting tumor cell glycolysis energy supply and depriving protein synthesis materials and energy source fatty acids.[116] This strategy is often used to induce metabolic stress in tumor cells, thereby enhancing the efficacy of other treatment methods. Autophagy, as a double-edged mechanism, can help cells decompose damaged organelles and promote tumor survival in harsh environments during mild nutrient deficiency.[117] However, under severe starvation, autophagy not only helps cells recover energy but may also degrade important structural or functional components within cells, ultimately leading to tumor cell death. Nanomaterials can serve as carriers for nutrient deprivation in starvation therapy and carry autophagy modulators to enhance treatment effects by regulating key signaling pathways and cellular stress responses. One such nanoparticle, LnNP@mSiO_2-GC, utilizes a mesoporous silica shell to enhance drug loading and a photosensitizer, Ce_6, to improve the effective excitation rate. It is designed to release the glycolysis inhibitor 2-deoxy-D-glucose (2DG) in response to the acidic tumor microenvironment.[118] In an *in vitro* evaluation using HCT116 colorectal cancer cells, cell survival significantly decreased to 63.9% under 980-nanometer irradiation, and to 16.3% at a high nanoparticle concentration (1000 μg mL^{-1}), demonstrating a potent tumor-killing effect. This research offers a new direction for colorectal cancer treatment, enabling more precise targeting of tumor cells, reducing side effects, and enhancing treatment efficacy.[119]

6.6 Artificial intelligence

Recent paradigm shifts in artificial intelligence (AI) large models have revolutionized scientific innovation, with medical applications covering various types such as machine learning (ML), deep learning (DL), and natural language processing (NLP). The synergistic integration of AI and nanotechnology has unveiled new dimensions in colorectal cancer (CRC) management. In ML domains, AI-optimized theranostic systems construct PDT/PTT sensitivity prediction models based on gene expression profiles, dynamically balancing synergistic effects between PDT/PTT and other therapies through supervised and reinforcement learning algorithms, while enabling real-time microenvironment monitoring. The integrated system achieves a real-time feedback control loop of "perception–decision–execution" with AI assistance: the perception layer continuously monitors tumor microenvironment parameters *via* nanosensors and transmits the data to the decision layer, where deep learning algorithms analyze the data, optimize parameter instructions, and predict optimal treatment plans. AI demonstrates significant advantages in processing complex data and image patterns.[120] Ultimately, AI-directed commands dynamically regulate therapeutic intensity at the execution layer, including light intensity, wavelength, and drug dosage.[121]

Furthermore, AI and ML play crucial roles in the production and regulation of nanomaterials. By leveraging extensive experimental data from literature, AI calculates quantitative parameters for nanodrugs and assists in model optimization to refine the toxicity and biological properties of nanostructures. Additionally, AI and ML enable remote monitoring through nanosensors, ensuring transparency in nanomaterial tracking and enhancing biosafety.[122] For early diagnosis, breathomics-based AI platforms employ ML-enhanced volatile organic compound (VOC) pattern recognition, correlating exhaled biomarkers with tumor redox statusto achieve non-invasive CRC screening and PDT/PTT resistance prediction.[123] Jung's team developed a plasmonic gold nanopolyhedron (AuNH)-integrated endoscopic platform incorporating surface-enhanced Raman scattering (SERS) sensors, enabling label-free CRC detection through colonic mucus analysis, with ML algorithms achieving 93.3% specificity in spectral data interpretation.[124] Furthermore, microbial robotics innovations yielded VA-SAM@BTO microrobots combining *Veillonella atypica*'s hypoxic targeting with piezoelectric $BaTiO_3$ nanocubes.[125,126] Under ultrasonic activation, these systems reprogram lactate metabolism, alleviate TME immunosuppression, and synergistically enhance PDT/PTT-induced immunogenic cell death (ICD). This multimodal data integration framework—incorporating Raman spectra, microbial metabolomics, and breath biomarkers—establishes closed-loop intelligent systems where AI dynamically optimizes illumination parameters (wavelength/intensity), nanocarrier delivery strategies, and combination therapies based on real-time molecular feedback.

Although AI/ML models have made significant contributions to theranostics, most currently available public datasets predominantly cover single populations with inadequate representativeness. This limitation may lead to data bias, failure to identify appropriate target populations, and insufficient sample sizes that cannot adequately reflect the molecular subtype diversity of CRC.[127] When model complexity is mismatched with data diversity, models may merely memorize the limited development set while lacking comprehension of tumor biological essence. In clinical practice, variables in materials, equipment, and disease progression can further contribute to model failure. Furthermore, these algorithms exhibit excessive dependence on data quality. For instance, as mentioned earlier, breathomics analysis is susceptible to interference from dietary factors and medications, while AI models overly rely on fixed-quality data. Additionally, tumor microenvironment detection may be compromised by tumor heterogeneity and variations in biopsy regions, resulting in data distortion.[128] Therefore, the application of such algorithms requires well-defined regulatory guidelines and corresponding quality control standards. Datasets employed must ensure high quality, comprehensiveness, and diversity. During data collection, patients should be fully informed of potential benefits and risks, with informed consent obtained and privacy protected to maximally eliminate data interference. The integration of spatial transcriptomics and single-cell sequencing technologies is recommended to acquire multidimensional data from different tumor regions. AI/ML models also demand extensive data for training and evaluation. With sufficiently robust datasets, the medical applications of these algorithms will become more comprehensive and beneficial.[129] From early detection to precision therapy modulation, these advancements exemplify innovative paradigms in intelligent nanomedicine, foreshadowing transformative breakthroughs through deeper AI-medical integration.

7 Conclusion

In summary, the application of nanomaterials in PDT and PTT has greatly expanded the selection of potential photosensitizers and targeting strategies, providing excellent results for the local treatment of colorectal cancer. The future development of precision nanomaterials presents multidimensional challenges and transformative opportunities. The paradigm shift from "universal nanoplatforms" to "precision nanoarchitectures", achieved through integration of patient-specific TME multi-omics profiling, enables spatiotemporal precision modulation of oncogenic signaling pathways. This engineered strategy based on individualized TME characteristics not only promises to overcome current therapeutic limitations but also aligns with the global trend of personalized cancer therapy within the precision medicine framework. At present, clinical transformation is still the biggest difficulty of nanomaterials, and it is hoped that more nanoparticles can be used in clinical practice in the future.

Abbreviations

AA	Aniline
AI	Artificial intelligence
ALP	Alkaline phosphatase
APC	Antigen-presenting cell
CDT	Chemodynamic therapy
CEA	Carcinoembryonic antigen
CQDs	Carbon quantum dots
CRGD	Cyclic arginine–glycine–aspartic acid
DAMP	Damage-associated molecular pattern
EPR	Enhanced permeability and retention effect
GGT	Gamma-glutamyl transferase
GSH	Glutathione
HA	Hyaluronic acid
HSP	Heat shock protein
ICD	Immunogenic cell death
MCNT	Multi-walled carbon nanotube
MI	Machine learning
MMPs	Matrix metalloproteinases
MOF	Metal–organic framework
NIR	Near-infrared
NPs	Nanoparticles
OXA	Oxaliplatin
PAI	Photoacoustic imaging
PCE	Photothermal conversion efficiency
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PLGA	Poly (lactic-*co*-glycolic acid)

PS	Photosensitizer
PTT	Photothermal therapy
QC	Quercetin
ROS	Reactive oxygen species
SPR	Surface plasmon resonance
TME	Tumor microenvironment
TNR	Tumor-to-normal ratio
UV	Ultraviolet
VEGF	Vascular endothelial growth factor

Data availability

No additional data are available.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors declare that they have no competing interests.

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