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Original Article

Progress in the Application of Nanomedicine in the Treatment of Colorectal Cancer and its Liver Metastasis Based on Targeted Therapy Strategy

Jingyi Xia[1], Tongtong Li[1], Shenzhen Zhou[1], Haofeng Ding[1, 2], Yun Sun[1, 2], Junwei Han[3], Congli Zhang[4*], Li Ren[3*]

[1]**Anhui Provincial Key Laboratory of Tumor Evolution and Intelligent Diagnosis and Treatment, Bengbu medical university**

[2]**Anhui Provincial Key Laboratory of Tumor Evolution and Intelligent Diagnosis and Treatment, Bengbu medical university, Bengbu 233030, China**

[3]**Department of Nuclear Medicine, School of Laboratory Medicine, Bengbu Medical University, Bengbu Bengbu 233030, China**

[4]**Department of Anesthesiology, First Affiliated Hospital of Bengbu Medical University, Bengbu 233004, China**

***Corresponding Author: Zhang Congli, Ren Li**

Abstract:
Colorectal cancer (CRC) is the third most common malignancy worldwide. Conventional treatments such as surgery, radiotherapy, and chemotherapy face limitations including recurrence, drug resistance, and side effects. Nanomedicine has improved targeting precision and therapeutic efficacy, representing an innovative strategy against CRC. This review highlights recent advances in nanomedicine targeting key CRC signaling pathways, such as Wnt/β-catenin, TGF-β/Smads, JAK-STAT, Ras-Raf-MAPK, and PI3K-Akt-mTOR. Given that the liver is the predominant site of metastasis and greatly increases mortality, focus is placed on nanomedicine for managing colorectal cancer liver metastases (CRCLM), including strategies targeting glycolytic metabolism, exosome communication, and immune cell regulation. Additionally, nanoparticle-based diagnostics enable early detection and multimodal imaging. This article synthesizes developments in nanomedicine for improved diagnosis, treatment, and liver metastasis control in CRC, aiming to promote comprehensive therapeutic strategies.

Keywords: Nanomedicine, CRC, CRCLM, targeted therapy

1. Introduction

CRC is the third most common malignancy globally, accounting for approximately 10% of all cancer cases, and is the second leading cause of cancer-related deaths worldwide. Early detection remains challenging due to the lack of noticeable symptoms in initial stages. Diagnosis typically occurs between ages 65 and 74, with most patients presenting at intermediate to advanced stages of the disease[12].In 2020, the global lifetime risk of developing and dying from gastrointestinal cancers was 8.20% and 6.17%, respectively. Colorectal cancer (CRC) posed the highest risk, accounting for 38.5% of total gastrointestinal cancer incidence and 28.2% of related deaths[3]. Conventional CRC treatments—surgery, radiotherapy, and chemotherapy—remain the cornerstone of therapy but are limited by recurrence, drug resistance, and damage to healthy tissues, driving the need for alternative strategies. Recent progress in immunotherapy,

targeted therapy, and multimodal regimens has expanded therapeutic options. Notably, nanomedicine has emerged as a promising approach to enhance drug targeting and retention, improving treatment efficacy and outcomes[4].The liver constitutes the predominant metastatic site and is the principal cause of mortality among CRC patients[56].Therefore, elucidating the role and mechanisms of nanomedicine in CRC and its liver metastases is crucial. This review systematically summarizes recent advances in nanomedicine for CRC, providing new insights for early diagnosis, treatment, and management of liver metastases.

2. Targeted Treatment of CRC with Nanomedicine

CRC is a highly heterogeneous disease driven by dysregulated molecular pathways. Key signaling cascades involved in its pathogenesis include Wnt/β-catenin, TGF-β/Smad, JAK/STAT, Ras/Raf/MAPK, and PI3K/Akt/mTOR[78]. This section reviews advances in nanomedicine strategies targeting these pathways for CRC treatment.

2.1 Nanomedicine Targeting the Wnt/β-catenin Signaling Pathway

The Wnt/β-catenin pathway is essential for intestinal stem cell maintenance and epithelial organization. Its dysregulation, particularly nuclear β-catenin accumulation, drives colorectal carcinogenesis. Mutations in APC predispose to familial adenomatous polyposis (FAP), while CTNNB1 mutations increase hereditary non-polyposis CRC (HNPCC) risk[910]. Therapeutic strategies aim to directly inhibit β-catenin nuclear translocation or indirectly modulate its degradation [1112].

AXIN2, a key component of the β-catenin destruction complex, is regulated by ALKBH5 through m^{6}A-dependent mRNA modification, leading to Wnt/β-catenin hyperactivation and CRC progression[1314]. Targeting this mechanism, Zhai et al. developed PLGA-based vesicles (VNP) encapsulating ALKBH5-targeted siRNA. Delivered via tail vein injection in multiple murine models, VNP suppressed β-catenin signaling by stabilizing AXIN2, thereby inhibiting colorectal tumor growth[15].

Salinomycin (SAL), an early cancer stem cell (CSC) inhibitor, targets the Wnt/β-catenin pathway but suffers from poor solubility and high toxicity[16]. To address this, Wang et al. developed salinomycin nanocrystals (SAL NCs), which in HT29 and HCT116 cells inhibited Wnt/β-catenin signaling by disrupting β-catenin/TCF4 interaction[17].

Additionally, curcumin has demonstrated potential as a modulator of the Wnt/β-catenin pathway. It facilitates caspase-3-mediated degradation of β-catenin and E-cadherin, reduces transcriptional activation by the β-catenin/TCF/LEF complex, and decreases its promoter-binding affinity[18]. Collectively, these actions inhibit Wnt signaling, leading to G2/M phase cell cycle arrest and apoptosis in CRC cells. A comprehensive summary of curcumin-based nanomedicines and their therapeutic effects in CRC is provided in Table 1, with the mechanistic pathway depicted in Figure 1.

Table. 1 Nanomedicines related to curcumin and its advantages

Nano-carriers	Advantages
cRGD-（CUR-CD＋DOX）-LPs（2:1）[19]	It can promote cell apoptosis and reverse multidrug resistance
Cso-sa/Cur micelles[20]	It can selectively kill CSCS and has low toxicity to live animals
Methoxy polyethylene glycol (MPEG) micelles[21]	Inhibit the proliferation and angiogenesis of tumor

Interpenetrating Polymer Network-Nitroglycerin (IPN-NGs) Nanogels[22]	Curcumin-loaded nanogels exhibit pH-sensitive properties, resulting in better stability of the nanogels at physiological pH (pH 7.4)
Au-CRC-TRC-NPs[23]	Controlled release of curcumin and offers a potential new approach to radiofrequency-assisted cancer therapy
Hyaluronic acid- camptothecin/curcumin nanoparticles (HA-CPT/CUR NP)[24]	It can infiltrate and accumulate in colon tumors and can not accumulate in adjacent healthy colon tissue
Cur@HKUST-1@PVP[25]	In vivo chemotherapy/photothermal therapy for colon cancer can be realized

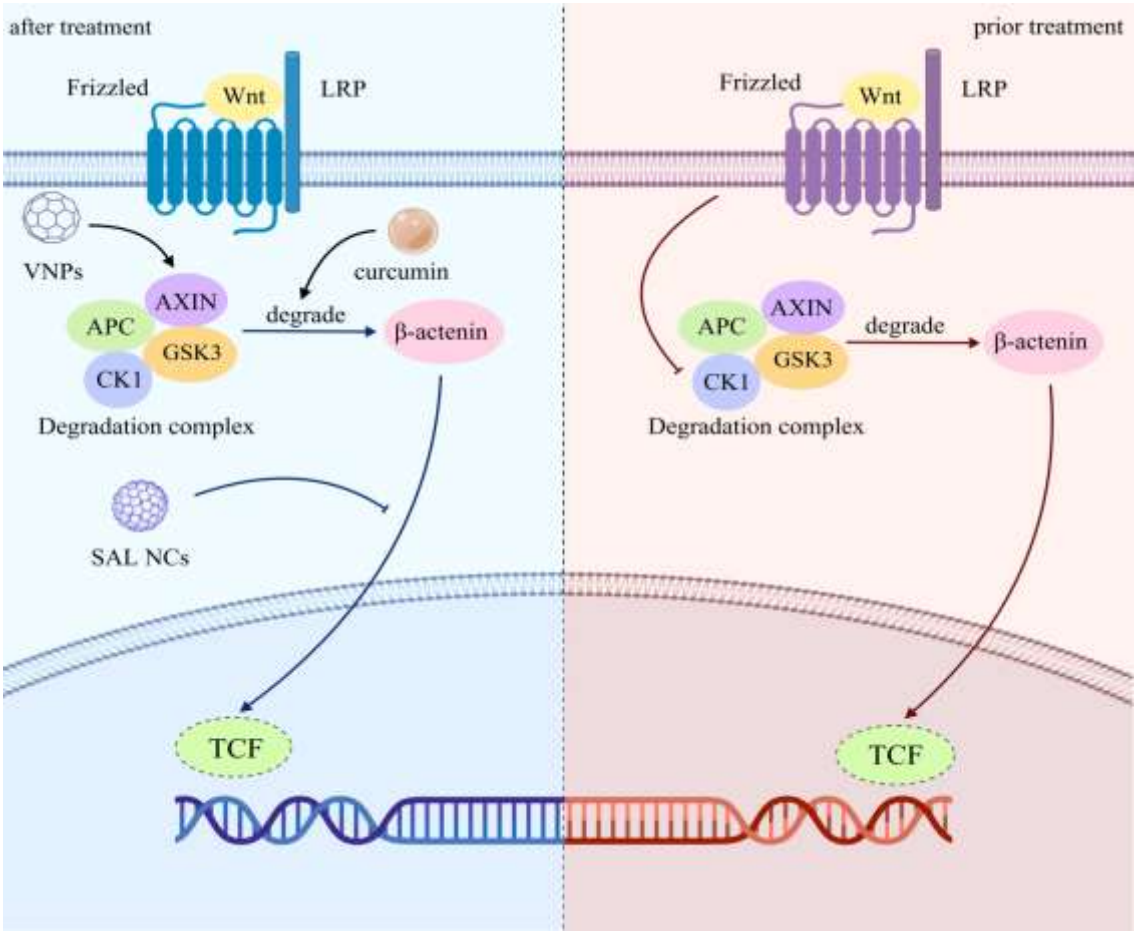

Fig.1 Mechanism of nanomedicines related to curcumin in Wnt pathway

2.2 Nanomedicines Targeting the TGFβ-Smads Signaling Pathway

The TGFβ–Smad signaling pathway regulates key cellular processes including proliferation, differentiation, migration, and apoptosis. Genetic alterations in components such as TβRII, TβRI, Smad2, and Smad4 are strongly linked to CRC pathogenesis. The frequent loss of β2SP and Smad4 in advanced and metastatic CRC further highlights the critical role of this pathway in CRC progression[2627].

Jin et al. developed a carbon nanotube (CNT)-based nanomedicine named CNT-CpG, which was delivered via intraperitoneal injection to CT26 tumor-bearing mice. The system significantly suppressed TGF-β-induced

epithelial–mesenchymal transition (EMT) and inhibited nuclear translocation of SMAD2/3. By targeting the TGF-β/Smad pathway, CNT-CpG effectively attenuated both primary colorectal tumor growth and hepatic metastases[28].

Huang et al. developed a multifunctional nanomedicine (NCG) using a PEG–PDPA copolymer to co-encapsulate chlorin e6 (Ce6) and galunisertib (Gal) via nanoprecipitation. In HCT116 xenograft mice administered intraperitoneally, NCG combined sonodynamic and chemotherapeutic effects to suppress tumor growth via TGFβ inhibition, demonstrating enhanced tissue retention and penetration with promising clinical applicability[29]. The mechanistic framework underlying the action of this nanomedicine is depicted in Figure 2.

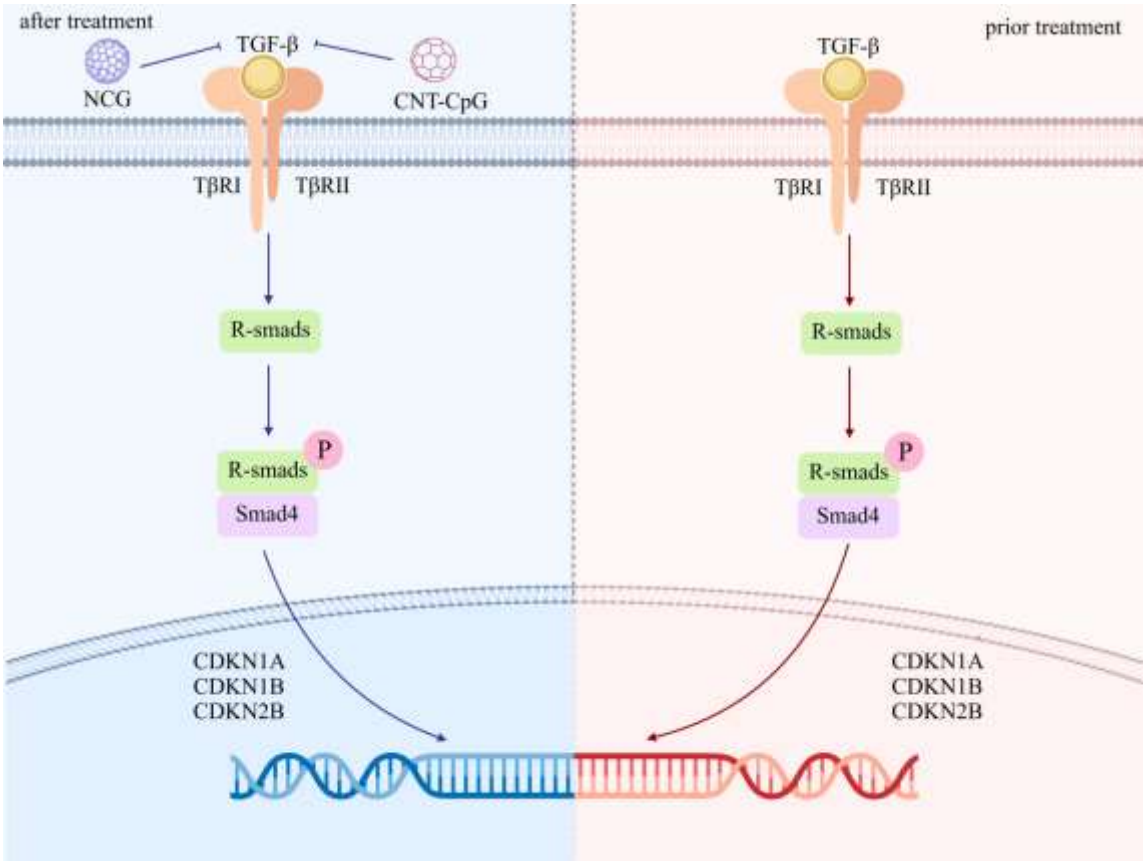

Fig.2 Mechanism of TGF β-Smads pathway-related nanomedicine

2.3 Nanomedicines Targeting the Jak-STAT Signaling Pathway

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway constitutes a vital intracellular mechanism responsible for regulating diverse biological functions, including cellular proliferation, differentiation, and immune modulation. Aberrant activation of this pathway has been strongly implicated in the pathogenesis and progression of CRC[3031].

Li et al. developed an oral inulin-based hydrogel system incorporating hollow MnO_2 nanoparticles loaded with oxaliplatin (Oxa@HMI), which targets the gut microbiota and modifies its composition. In a murine orthotopic CRC model, Oxa@HMI significantly reduced the abundance of the pathogenic Alistipes genus, which promotes tumor progression via IL-6/STAT3 signaling. By suppressing this JAK-STAT pathway and enhancing mucoadhesion and gastrointestinal retention through the inulin

coating, Oxa@HMI demonstrates strong therapeutic potential against CRC[32]. A schematic representation of the underlying mechanism is provided in Figure 3.

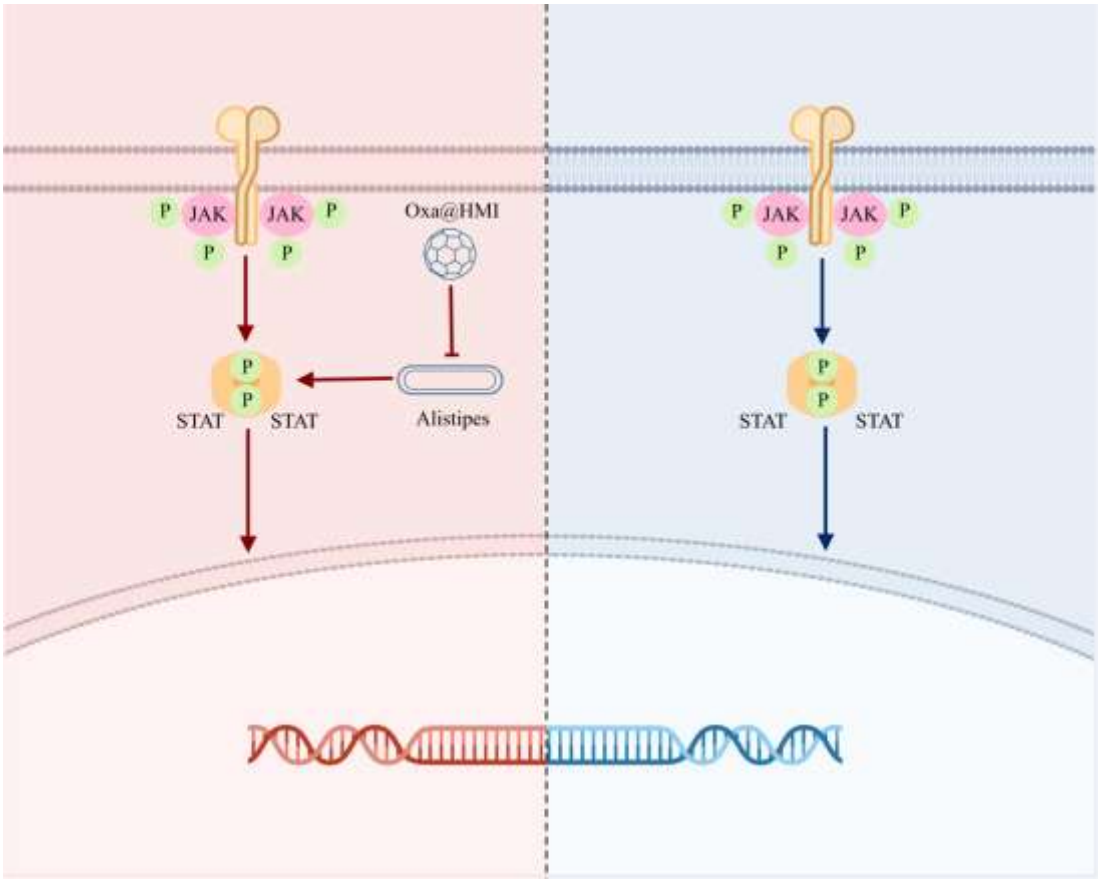

Fig.3 Principle of Oxa@HMI in the Jak-STAT pathway

2.4 Nanomedicines Targeting the Ras-Raf-MAPK Signaling Pathway

The Ras-Raf-MAPK pathway plays a critical role in regulating cell proliferation, and its dysregulation is strongly associated with CRC development. Mutations in RAS and BRAF are found in approximately 36% and 9–11% of CRC cases, respectively. In this pathway, MEK activates ERK through phosphorylation, influencing multiple essential cellular processes[33].

Yu et al. developed FexMoyS-PEG nanoparticles containing multivalent Fe/Mo ions, which catalyze H_2O_2 conversion into hydroxyl radicals (•OH), leading to MEK and ERK phosphorylation. In two murine models—patient-derived xenografts in NSD mice and HCT116 xenografts in nude mice—intravenous administration of these NPs downregulated key MAPK pathway proteins (c-Myc, p-MEK1/2, p-ERK1/2), indicating suppression of colorectal tumor growth via MAPK pathway inhibition [34].

Building on Yu et al.'s research, Bian et al. developed a TME-responsive nanocomposite, MnDIG@PEG, for co-delivering the IDO inhibitor Epacadostat (IDOi) and glucose oxidase (GOx). Mn_3O_4 catalyzed H_2O_2 decomposition to produce oxygen, which enhanced GOx-driven glucose consumption and H_2O_2 generation. This cascade amplified •OH production via Mn^{2+}, inducing MEK/ERK phosphorylation and suppressing CRC progression.[34]. The proposed mechanism is depicted in Figure 4.

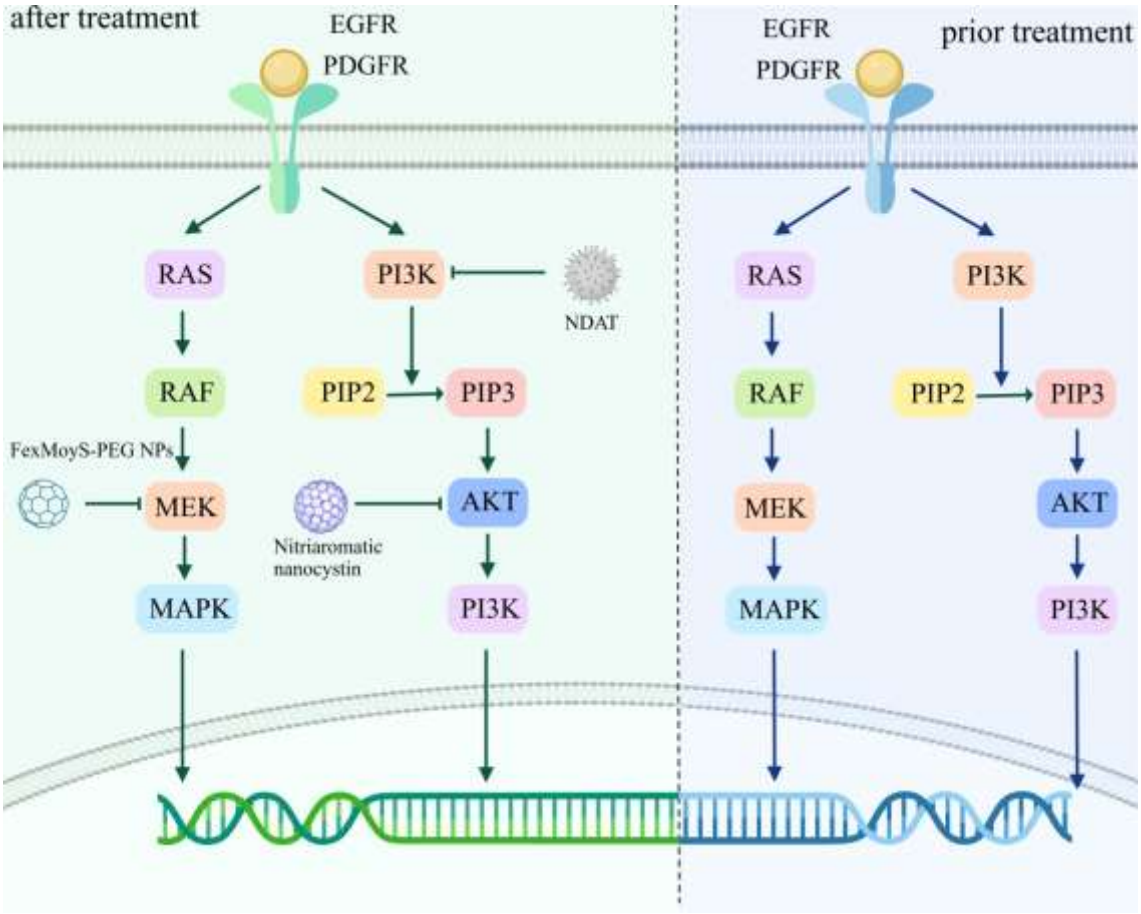

Fig.4 Principle of action of the above nanomedicines in PI3K-Akt-mTOR, Ras-Raf-MAPK pathways.

2.5 Nanomedicines Targeting the PI3K-Akt-mTOR Signaling Pathway

The PI3K-Akt-mTOR pathway is a key intracellular signaling cascade regulating cell proliferation, apoptosis, angiogenesis, and glucose metabolism. Its aberrant activation promotes CRC growth, metastasis, and epithelial-mesenchymal transition (EMT)[36].Notably, PI3K upregulates PD-L1 expression, enhancing immune evasion and metastatic potential, while Akt amplifies PI3K signaling, making both molecules critical therapeutic targets in CRC[37].

In this context, Huang et al. reported that the nanomedicine NDAT effectively inhibited PI3K activation in HCT116 CRC cells, leading to a reduction in PD-L1 expression and demonstrating therapeutic efficacy against CRC[38].

Zhang et al. developed an Akt-targeting nitroaromatic nanocystin, which was tested on HCT8, HCT116, and LoVo CRC cells. The compound selectively inhibited AKT1, markedly suppressing CRC proliferation, and demonstrated favorable tolerability, highlighting its potential as a therapeutic agent for CRC[39].The mechanistic pathways underlying the action of these nanomedicines are depicted in Figure 4.

3. Advances in Targeted Therapy with Nanomedicines for CRCLM

Despite significant advances in the diagnosis and treatment of colorectal cancer (CRC), metastasis remains the leading cause of death. Consistent with Stephen Paget's "seed and soil" hypothesis, the liver serves as the predominant site for CRC metastasis[4041]. Nevertheless, a thorough review focusing on the application of nanomedicines for the management of CRCLM remains absent. This article aims to provide a comprehensive overview of recent advancements in this area.

3.1 Targeting Glycolysis

Glycolysis facilitates the adaptation of CRC cells to the hypoxic microenvironment of the liver by employing the "Warburg effect" as a primary mechanism for energy generation. Moreover, the lactic acid produced through glycolytic processes contributes to tumor angiogenesis and immune system evasion[4243].

In a study by Wang et al., betulinic acid-loaded nanoliposomes (BA-NLs) were synthesized and applied to HCT116 cell cultures at varying concentrations. The findings revealed that BA-NLs markedly suppressed both the proliferation and glucose uptake of CRC cells by targeting critical regulators and pathways associated with glycolysis and fatty acid metabolism. Additionally, BA-NLs effectively inhibited the hepatic metastasis of CRC[44].

Lei et al. developed folate receptor-targeted nanoparticles loaded with α-tocopherol succinate and 2-deoxy-D-glucose (TDF NPs) for treating colon adenocarcinoma. In this system, 2-DG inhibits glycolysis, while α-TOS suppresses mitochondrial oxidative phosphorylation (OXPHOS). Evaluated in HT29 cells, TDF NPs demonstrated significant antitumor efficacy with low hepatotoxicity, highlighting their potential for targeting dysregulated energy metabolism in CRCLM[45].

3.2 Targeting Exosomes

Exosomes secreted by primary tumor cells have the capacity to migrate to distant metastatic sites, where they modulate the pre-metastatic tumor microenvironment through various signaling pathways and contribute to immune regulation. These vesicles are integral to intercellular communication in both physiological and pathological contexts, facilitating processes such as angiogenesis, epithelial-mesenchymal transition (EMT), CRC progression, and the formation of pre-metastatic niches[4647].

Deng et al. demonstrated that circSKA3 inhibits exosome release in CRC by retaining oncogenic circRNAs intracellularly, thereby increasing cellular stability. Using antisense oligonucleotides (ASOs) against circSKA3 in a CRCLM mouse model (established via intrasplenic injection of HCT116 cells), they showed that ASO knockdown promoted the export of oncogenic circRNAs via exosomes and reduced liver metastasis. Additionally, ASOs disrupted the circSKA3–SLUG interaction, inhibiting epithelial–mesenchymal transition (EMT). These findings suggest a potential therapeutic strategy for CRC[48].

3.3 Targeting Immune Cells

The interaction between immune cells and cancer cells shapes the tumor immune microenvironment (TME), critically influencing metastasis, survival, and post-metastatic growth—especially in CRCLM[49].Immunotherapy activates anti-tumor immunity, enhances systemic immune surveillance, suppresses local and distant metastases, and establishes lasting immune memory to prevent recurrence. Current strategies largely focus on cytokine-targeting approaches and immune cell modulation, including macrophages, dendritic cells, and T lymphocytes [50].

Wang et al developed acid-activated micellar complexes (POP micelles) via nanoprecipitation and delivered them intravenously to B16-F10 tumor-bearing C57BL/6 mice in combination with photodynamic therapy (PDT). The nanomedicine downregulated PD-L1 expression, disrupting the PD-1/PD-L1 immunosuppressive axis. Additionally, the combination of PDT and POP micelles enhanced the host immune response by increasing secretion of pro-inflammatory cytokines, including TNF-α and IFN-γ, contributing to the inhibition of CRCLM [51].

Mao et al. developed a macrophage-targeted nanomedicine, LNT-UA, via nanoprecipitation of ursolic acid (UA) and Ganoderma lucidum

polysaccharide (LNT). Evaluated in multiple murine models—including subcutaneous CT26, bilateral dorsal, and AOM/DSS-induced spontaneous CRC—LNT-UA promoted dendritic cell maturation, shifted macrophages from M2 to M1 phenotype, and triggered immunogenic cell death, demonstrating efficacy against CRCLM[52].

Ni et al. developed dual-adjuvant nanovaccines (banNVs) for colorectal cancer immunotherapy by synthesizing Primer-PEG-PLA nanoparticles combined with CpG oligonucleotides to form microfibers, which were then integrated with the immunostimulant R848. Administered subcutaneously in MC38 tumor-bearing C57BL/6 mice, the banNVs effectively activated dendritic cells and enhanced cytotoxic T lymphocyte responses, demonstrating significant efficacy against CRCLM[53].

Lang et al. developed orally administered prebiotic nanoparticles (SCXN) that modulate the CRC immunosuppressive microenvironment by preserving cytotoxic T lymphocyte function and reducing CD4+Foxp3+ Tregs, significantly suppressing CRCLM in mice[54].To enhance CAR-T cell efficacy against solid tumors, FA_IL/CCL nanospheres—composed of folic acid-modified magnesium silicate loaded with IL-2, IL-15, and CCL5—were constructed. These nanoparticles increased the immunogenicity of CD46-targeted CAR-T cells, effectively inhibiting tumor growth and liver metastasis in CRC PDX models[55].

4. The Value of Nanomedicines in the Diagnosis of CRC

CRC is often diagnosed at an advanced stage due to the subtlety of early symptoms, which leads to delayed detection and treatment. Consequently, enhancing the precision of early diagnostic methods is critical. Nanomedicine has shown considerable promise in improving diagnostic accuracy for CRC[5657].

Conventional ^{1}H MRI provides high soft-tissue resolution but suffers from a short half-life, necessitating repeated injections for monitoring CRCLM. To address this, Li et al. developed C-Met-targeting peptide-functionalized perfluorinated crown ether nanoparticles (AH11 1972-PFCE NPs). These nanoparticles exhibit high sensitivity for early CRC detection and maintain tumor retention for over seven days, enabling continuous therapy monitoring[58].

In another study, Yang et al. engineered magnetic nanoparticles conjugated with antibodies targeting carcinoembryonic antigen (CEA). This magnetic reagent enabled the detection of CEA molecules in serum samples. Analysis of serum from 24 healthy individuals and 30 colon cancer patients established a diagnostic threshold for serum CEA at 4.05 ng/mL, yielding a clinical sensitivity of 0.90 and specificity of 0.87 for CRC diagnosis[59].

Jia et al. developed gold nanorod@silica-carbon dot (GNR@SiO2-CD) nanocomposites by integrating carbon dots and gold nanorods on a silica scaffold. These nanostructures act as photothermal diagnostic agents for intravenous use, utilizing the high sensitivity and spatial resolution of fluorescence (FL) and photoacoustic (PA) imaging to guide photodynamic (PDT) and photothermal (PTT) therapy. Owing to their chemical stability, low toxicity, and enhanced imaging performance, they demonstrate significant potential for multimodal cancer imaging and early CRC detection[60].

5. On the latest advancements in 2025 for the treatment of CRC and CRLM

The following provides a summary of the latest advancements in 2025 for the treatment of CRC and CRLM. It is presented in three tables covering: novel therapeutic methods for CRC and CRLM（Table.2）, nanomedicine-based therapies for CRC (Table.3), and nanomedicine-based therapies for CRLM (Table.4).

Table. 2 Novel therapeutic approaches for CRC and CRLM

Method	CRC Type
XTX101 combined with atezolizumab[61]	Immune "cold" tumors (MSS CRC)
cabozantinib and nivolumab[62]	Refractory, microsatellite stable (MSS) metastatic CRC patients
Neoadjuvant immunotherapy[63]	dMMR/MSI-H locally advanced CRC patients
Nelmastobart (hSTC810) combined with capecitabine therapy[64]	Metastatic CRC resistant or intolerant to oxaliplatin and irinotecan chemotherapy
QL1203 vs placebo plus mFOLFOX6[65]	RAS wild-type metastatic CRC
cabozantinib in combination with panitumumab[66]	Metastatic CRC patients with MET amplification

Table. 3 Nanomedicine for CRC

Nano-carriers	advantages
COF-FA@DOX[67]	Effectively internalized by SW480 CRC cells and demonstrated significantly higher cytotoxicity
CP@MSN/PB@CWL[68]	Significantly enhanced penetration efficiency through the intestinal mucus and epithelial barriers
NEs-PTX-BEZ235[69]	Inhibited drug-resistant proteins, reduced drug resistance, suppressed tumor stemness, and induced apoptosis in colon CRC
miR-497-loaded SPION@Ag@Cs[70]	Targeted the miR-497/CTLA4 axis for CRC treatment via an immunotherapy strategy
OXA@Exo-RD[71]	Induced mitochondrial-mediated apoptosis and dysfunction, providing an attractive strategy for treating drug-resistant CRC
Tau/CDs[72]	Targeted heme oxygenase-1 (HO-1) to mediate ferroptosis for CRC treatment
CUPIT NPs[73]	Quantified pyroptosis in vitro and provided guidance for pyroptosis-mediated tumor therapy in vivo, minimizing systemic side effects

Table. 4 Nanomedicine for CRLM

Nano-carriers	advantages
OEMH NPs[74]	Suppressed liver metastasis by blocking the transformation of hepatic stellate cells (HSCs) into cancer-associated fibroblasts (CAFs)
NM@PLGA-MTI-OXA[75]	Effectively addressed the clinical drawbacks of traditional antibiotics disrupting gut microbiota balance and poor targeting of chemotherapeutics, inhibiting CRC and CRLM
DMSN@Pla-Lipo[76]	Translocated to metastatic lymph nodes via tumor lymphatics, eradicating metastatic tumor cells in lymph nodes; metastases in other major organs were also suppressed
miRNA@sEVs[77]	Downregulated FSCN1 protein expression, demonstrating significant inhibition of CRC tumor progression both in vitro and in vivo
CCM-FSS&CHM-ABI[78]	A dual-targeting nano-system that synergistically inhibited CRLM by inducing tumor cell ferroptosis and CAF reprogramming
Ev-siCCL24 and Ev-siNC[79]	Proposed a potential therapeutic alternative for CRC patients with treatment resistance and distant metastasis

6. Conclusion

CRC, a highly heterogeneous malignancy, is witnessing a transformation in treatment strategies through advances in nanotechnology. Nanomedicines offer novel avenues for CRC therapy, demonstrating strong potential to enhance therapeutic efficacy and reduce side effects due to their unique physicochemical properties. This review explores the targeted molecular mechanisms of nanomedicines against CRC and its liver metastases, as well as their diagnostic applications. Future efforts should focus on optimizing nanomedicines to improve diagnostic and therapeutic performance, enhance safety and efficacy, and promote personalized treatment approaches for CRC.

Statements & Declarations

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Competing Interests

The authors declare that they have no competing interests.

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