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REVIEW

Recent advances and challenges in colorectal cancer: From molecular research to treatment

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Abstract

Colorectal cancer (CRC) ranks among the top causes of cancer-related fatalities globally. Recent progress in genomics, proteomics, and bioinformatics has greatly improved our comprehension of the molecular underpinnings of CRC, paving the way for targeted therapies and immunotherapies. Nonetheless, obstacles such as tumor heterogeneity and drug resistance persist, hindering advancements in treatment efficacy. In this context, the integration of artificial intelligence (AI) and organoid technology presents promising new avenues. AI can analyze genetic and clinical data to forecast disease risk, prognosis, and treatment responses, thereby expediting drug development and tailoring treatment plans. Organoids replicate the genetic traits and biological behaviors of tumors, acting as platforms for drug testing and the formulation of personalized treatment approaches. Despite notable strides in CRC research and treatment - from genetic insights to therapeutic innovations - numerous challenges endure, including the intricate tumor microen-vironment, tumor heterogeneity, adverse effects of immunotherapies, issues related to AI data quality and privacy, and the need for standardization in organoid culture. Future initiatives should concentrate on clarifying the pathogenesis of CRC, refining AI algorithms and organoid models, and creating more effective therapeutic strategies to alleviate the global impact of CRC.

Key Words: Colorectal cancer; Molecular; Treatment; Artificial intelligence; Organoid

Core Tip: This study highlights recent advances and challenges in colorectal cancer from molecular research to treatment. Advances in genomics, proteomics, and bioinformatics have significantly enhanced our understanding of colorectal cancer's molecular mechanisms, driving targeted therapies and immunotherapies. However, tumor heterogeneity and drug resistance remain major hurdles. Artificial intelligence and organoid technology offer new opportunities.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors in the digestive system, ranking third in incidence (9.6%) and second in mortality rate (9.3%) worldwide in 2022[1,2]. It poses a significant threat to the public[3]. The rising incidence of CRC can be attributed to lifestyle changes, such as reduced physical activity and a higher intake of high-fat foods[4]. By 2030, it is projected that there will be more than 2.2 million new cases of CRC worldwide, with an estimated 1.1 million deaths, further exacerbating the global health burden[5].

CRC progresses from normal epithelial cells through a process of uncontrolled growth, leading to the formation of polyps and ultimately cancer. Adenocarcinoma is the predominant subtype. The genetic landscape of CRC is complex, involving various molecular pathways that contribute to tumor development and metastasis[6]. Current treatment modalities include surgery, chemotherapy, radiotherapy, and targeted therapies[7]. Surgical intervention is typically favored for early-stage CRC, while patients with advanced disease often require a combination of therapies. However, these treatment options have their drawbacks: Chemotherapy can lead to adverse effects such as nausea and hair loss, and tumor cells may develop resistance to drugs. Immunotherapy can boost immune responses but is primarily effective for a limited group of patients[8]. Targeted therapies aim to inhibit specific mutations but are restricted to individuals with particular genetic alterations and may encounter secondary resistance. Overall, existing treatment strategies do not fully address clinical needs, as treatment outcomes remain suboptimal, recurrence rates are high, and patients' survival and quality of life are significantly impacted[9].

"Precision medicine" emphasizes personalized approaches to disease diagnosis, treatment, and prevention by considering individual variations. It employs omics technologies, including genomics and proteomics, to analyze, identify, validate, and apply biomarkers for large populations and specific diseases. The objective is to identify disease causes and therapeutic targets while accurately subclassifying disease states and processes. In 2012, The Cancer Genome Atlas (TCGA) research network published a comprehensive molecular characterization of human CRC in Nature. This marked the third malignant tumor for which cancer genomic information was released by the TCGA project team, heralding the onset of the "precision medicine" era for CRC. The TCGA project utilizes molecular markers to develop models for prognosis and treatment guidance. In the realm of CRC, initial prognostic assessments were based on a limited number of markers, including chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP). Experts have since incorporated genetic mutations, copy number variations, methylation patterns, microRNA profiles, and proteomic data to categorize CRC into four consensus molecular subtypes (CMS)[10]: CMS1 (MSI immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal). The CMS classification system is now regarded as the most reliable framework for CRC, offering clear biological insights and guiding future clinical stratification and targeted interventions.

The integration of artificial intelligence (AI) in healthcare is rapidly advancing precision medicine[11]. Notable advancements include pathological diagnosis, imaging diagnostics, molecular diagnostics, personalized treatment, and drug discovery[12]. AI identifies new molecular markers and therapeutic targets by analyzing genomic, radiomic, and clinical data, thereby improving diagnostic accuracy and treatment effectiveness. AI can evaluate pathological images using deep learning (DL) algorithms, automatically detecting tumor cells and characteristics of the microenvironment, and assisting clinicians in diagnosis and classification[13]. Furthermore, AI can forecast a patient's response to various treatment options based on their genomic and clinical data, providing valuable insights for clinicians to formulate personalized treatment plans[14].

Despite the array of treatment options available for CRC, including surgery, chemotherapy, radiotherapy, and targeted therapies, these approaches encounter challenges such as drug resistance and insufficient personalized precision. Organoid technology addresses these challenges by accurately mimicking the tumor microenvironment in vitro, preserving tumor heterogeneity, and facilitating high-throughput drug screening[15]. Patient-derived tumor organoids (PDOs) replicate the genetic features of original tumors, improving evaluations of drug sensitivity and resistance while supporting personalized treatment strategies[16]. When combined with advanced techniques like single-cell sequencing and genome analysis, organoids offer a powerful platform for new drug development and predicting therapeutic outcomes, thereby advancing disease research[17]. In summary, organoid technology holds significant potential for enhancing CRC diagnosis and treatment.

With the swift progress in molecular pathology and the emergence of precision medicine, the development of individualized treatment plans has become a crucial priority to improve both survival rates and quality of life for

patients. This paper explores the molecular mechanisms underlying CRC, personalized treatment strategies, and the application of AI and organoids in the management of CRC.

GENETIC AND EPIGENETICS ALTERATIONS IN CRC

At the molecular level, CRC arises from the cumulative effects of polygenic and epigenetic alterations. Similar to other solid tumors, CRC exhibits significant heterogeneity, which can be attributed to at least three major molecular pathways: MSI, CIMP, and CIN[18]. From a therapeutic standpoint, MSI is linked to immunotherapy in CRC, while CIN and CIMP are not direct therapeutic targets; rather, they inform the selection of treatment strategies based on the specific gene mutations they induce. These pathways contribute to the progression of CRC through gene mutations, epigenetic alterations, and abnormal cell signaling mechanisms. The predominant pathway in CRC is CIN, which is present in approximately 85% of sporadic cases[19]. CIN can be divided into two categories: High-level CIN and low-level CIN. CIN is characterized by abnormal chromosome structure and number, loss of heterozygosity at tumor suppressor gene (TSG) loci, and chromosomal rearrangements, resulting in somatic copy number alterations (SCNA). These alterations are often associated with mutations in key genes such as adenomatous polyposis coli (*APC*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), B-raf proto-oncogene (*BRAF*), sma and mad homolog (*SMAD)*, and tumor protein 53 (*P53*)[20], which are crucial for regulating cell proliferation and the cell cycle, thus playing a significant role in CRC development. Another important pathway is MSI, which arises from the malfunction of DNA mismatch repair (MMR) genes during DNA replication and repair processes. This malfunction leads to a shift from microsatellite stability (MSS) to instability. MSI is often linked to a genetic predisposition characterized by high variability and can be further classified into high MSI (MSI-H) and low MSI (MSI-L). The third major pathway is CIMP. Tumors classified as CIMP-high (CIMP-H) exhibit *BRAF* mutations, MutL homolog 1 (MLH1) methylation, and silencing of *MGMT* or *CDKN2A*, whereas CIMP-low *(*CIMP-L*)* tumors are associated with *KRAS* mutations[21].

THE MECHANISM OF CRC OCCURRENCE AND DEVELOPMENT

The progression of CRC typically follows an adenoma-carcinoma-metastasis model (Figure 1), evolving from aberrant crypt foci to benign adenomatous polyps and ultimately to sporadic CRC over a span of 10 years to 15 years. This model is observed in 70% to 90% of cases. The malignant transformation involves three critical stages: Stem or epithelial cells acquire driver mutations; mutant cells outcompete wild-type cells to dominate the crypt (clonal fixation); and mutant crypts expand through crypt division (clonal expansion)[22]. These processes are linked to sequential mutations in genes such as *APC*, *KRAS*, and *TP53*. According to the multi-step genetic model proposed by Fearon and Vogelstein[23], the early inactivation of the TSG *APC* located on chromosome 5q21-q22 is essential. Mutations in *APC* lead to aberrant *Wnt/β-catenin* signaling[24,25], which promotes cell proliferation and inhibits apoptosis, a crucial step in benign polyp formation. CRC develops through the activation of proto-oncogenes and the inactivation of TSGs. *KRAS* mutations facilitate continuous signaling for cell growth and survival, driving the formation and expansion of adenomatous polyps. In advanced macroadenomas, additional driver mutations accumulate. The deleted in colorectal carcinoma gene influences cell adhesion pathways, impacting tumor progression. Mutations in *BRAF V600E*, *SMAD4/DPC4*, and alterations in the transforming growth factor beta (*TGF-β*) pathway affect cell migration and invasion. Changes in the phosphatidylinositol 3-kinase (*PI3K*) - protein kinase B (*AKT*) pathway, including mutations in *PIK3CA* and phosphatase and tensin homolog, lead to uncontrolled cell proliferation. Defects in *MMR* genes, such as *MLH1* and *MSH2*, result in MSI, producing tumors with unique clinical features and potentially improved prognosis. Collectively, these genetic alterations transform normal cells into cancer-associated fibroblasts (CAFs) and colon cancer stem cells, creating a signaling environment that fosters tumor growth. The final genetic alteration in the transition from advanced adenomas to aggressive cancers, as outlined in the Vogelstein model, is the inactivation of *P53*. Mutations in *P53* enable cells with accumulating genetic abnormalities to survive and proliferate, promoting the development and metastasis of aggressive cancers. Known as the "guardian of the genome", *P53* plays a vital role in DNA repair, cell cycle regulation, and apoptosis. These genetic changes also induce epigenetic alterations, particularly CIN. Hypermethylation silences TSGs, while hypomethylation leads to the overexpression of proto-oncogenes. The CIMP, characterized by frequent methylation events, is strongly associated with CRC.

Not all CRCs strictly adhere to this conventional pathway. Approximately 15% develop through the serrated pathway and exhibit distinct molecular characteristics (Figure 1). Serrated tumors can progress *via* two primary routes: The traditional serrated pathway and the sessile serrated pathway[26]. The traditional serrated pathway primarily occurs in the proximal colon, beginning with *KRAS* mutations. It progresses from hyperplastic polyps rich in goblet cells to traditional serrated adenomas (TSA). Methylation of *MGMT* and other TSGs leads to TSA with high-grade dysplasia. Further genetic alterations result in serrated adenocarcinoma (SAC), characterized by MSI-L/CIMP-L or MSS/CIMP-L, indicating aggressive CRC[27]. The sessile serrated pathway mainly affects the right-sided colon, starting with *BRAF* mutations. Microvesicular hyperplastic polyps progress to sessile serrated lesions (SSL). This progression involves MLH1 methylation and other TSG methylation events, advancing to SSL with high-grade dysplasia. Continued genetic changes culminate in SAC, characterized by MSI-L/CIMP-H or MSI-H/CIMP-H, which also indicates the presence of invasive CRC. In summary, both the traditional serrated pathway and the sessile serrated pathway are significant routes in colorectal carcinogenesis. These pathways exhibit higher rates of *BRAF* and *KRAS* mutations, increased CIN, and elevated

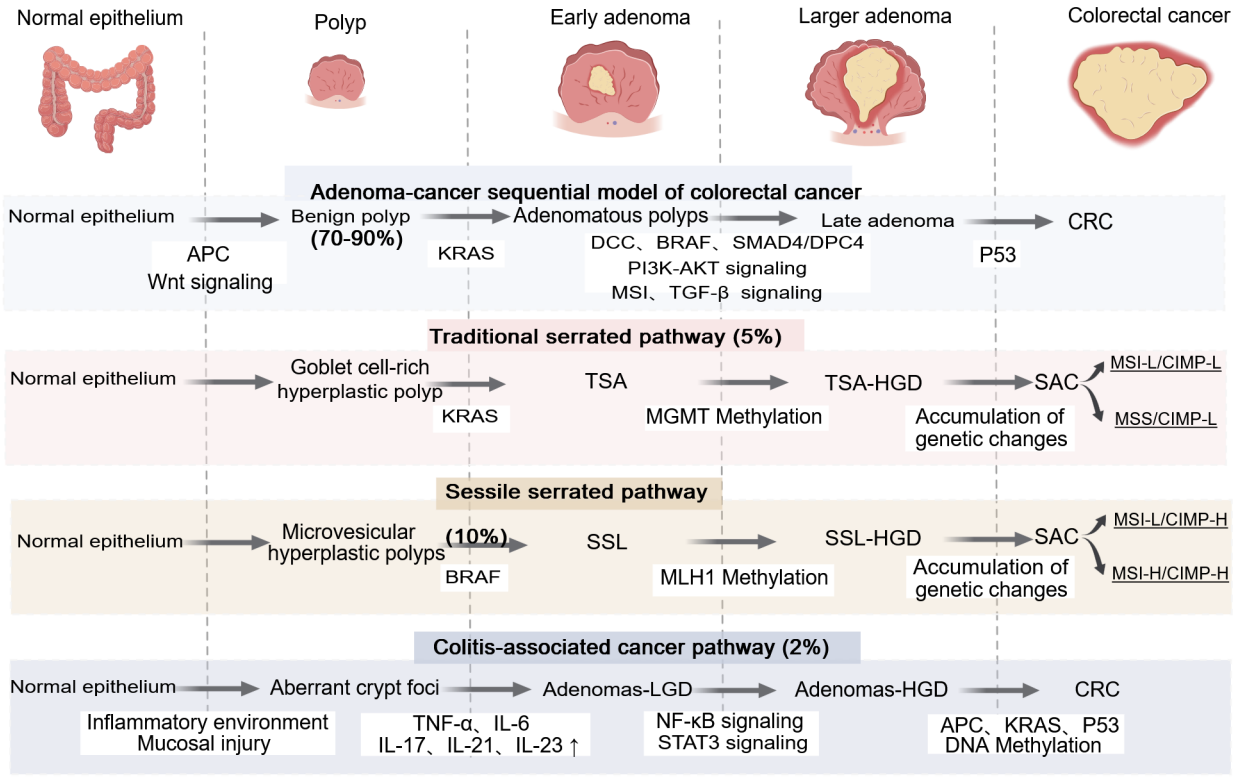

Figure 1 Four distinct pathways of progression from polyps to colorectal cancer, each characterized by specific molecular alterations. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. These pathways include the adenoma-carcinoma-metastasis sequence, the traditional serrated pathway, the sessile serrated pathway, and cancers associated with colitis. DCC: Deleted in colorectal cancer; BRAF: B-raf proto-oncogene; SMAD4: Sma and mad homolog; DPC4: Sma and mad homolog family member 4; MGMT: O-6-methylguanine-DNA methyltransferase; MLH1: MutL homolog 1; AKT: Protein kinase B; PI3K: Phosphatidylinositol 3-kinase; TGF-β: Transforming growth factor beta; MSI: Microsatellite instability; TGF: Transforming growth factor; CRC: Colorectal cancer; CIMP-H: CpG island methylator phenotype-high; CIMP-L: CpG island methylator phenotype-low; MSS: Microsatellite stability; MSI-H: High microsatellite instability; MSI-L: Low microsatellite instability; TSA: Traditional serrated adenomas; TSG: Tumor suppressor genes; TSA-HGD: Traditional serrated adenomas with high-grade dysplasia; SSL: Sessile serrated lesions; SSL-HGD: Sessile serrated lesions with high-grade dysplasia; CAC: Colitis-associated cancer; Adenomas-LGD: Adenomas with low-grade dysplasia; Adenomas-HGD: Adenomas with high-grade dysplasia; SAC: Spindle assembly checkpoint; TNF-α: Tumor necrosis factor-α; IL: Interleukin; NF-Kb: Nuclear factor kappa B; APC: Adenomatous polyposis col; KRAS: Kirsten rat sarcoma viral oncogene homolog; STAT3: Signal transducer and activator of transcription 3.

hypermutation rates, but they rarely involve *APC* mutations. Familial and hereditary CRCs, such as Lynch syndrome caused by germline MMR gene mutations, account for about 5% of cases and are often associated with MSI-H.

Colitis-associated cancer (CAC), a specific form of CRC, primarily affects patients with inflammatory bowel disease (Figure 1). CAC constitutes only about 2% of all CRC cases, and most patients with inflammatory bowel disease do not develop it[28]. Compared to sporadic or familial CRC, CAC shares both similarities and distinct features in etiology, genetic alterations, and treatment approaches[29]. Chronic intestinal inflammation, as observed in ulcerative colitis and Crohn's disease, elevates the risk of CAC in proportion to the duration and severity of the inflammation. Ongoing inflammation leads to DNA damage, activates inflammatory pathways such as nuclear factor kappa B (*NF-kappa B*) and signal transducer and activator of transcription 3 (*STAT3*), and induces mutations in critical genes including *P53*, *KRAS*, and *APC*. Epigenetic modifications, such as DNA methylation and alterations in MMR genes, contribute to dysplasia in epithelial cells. The regulation of the immune system fosters an immunosuppressive microenvironment that is conducive to tumor growth. As additional genetic and epigenetic changes accumulate, adenomas with low-grade dysplasia and those with high-grade dysplasia may progressively develop and ultimately progress to CAC.

SIGNIFICANT BIOLOGICAL DISTINCTIONS BETWEEN THE LEFT AND RIGHT-SIDED COLON

The distinction between right and left colon cancer is not uniformly defined. The most common classification identifies cancers located proximally to the splenic flexure as right-sided colon cancer, while those at or distal to the splenic flexure are classified as left-sided colon cancer (Figure 2). According to the CMS classification, left-sided colon cancers predominantly fall under the CMS2 subtype, which is associated with a more favorable prognosis, whereas right-sided colon cancers are primarily classified as CMS1, indicating poorer outcomes[30]. This classification reflects their embryonic origins: The proximal two-thirds of the transverse colon develop from the midgut, while the distal third originates from the hindgut[31]. Right and left colon cancers exhibit differences in embryonic origin, anatomical structure, and physiological function, leading to distinct genetic and epigenetic profiles[32]. These variations influence drug respons-

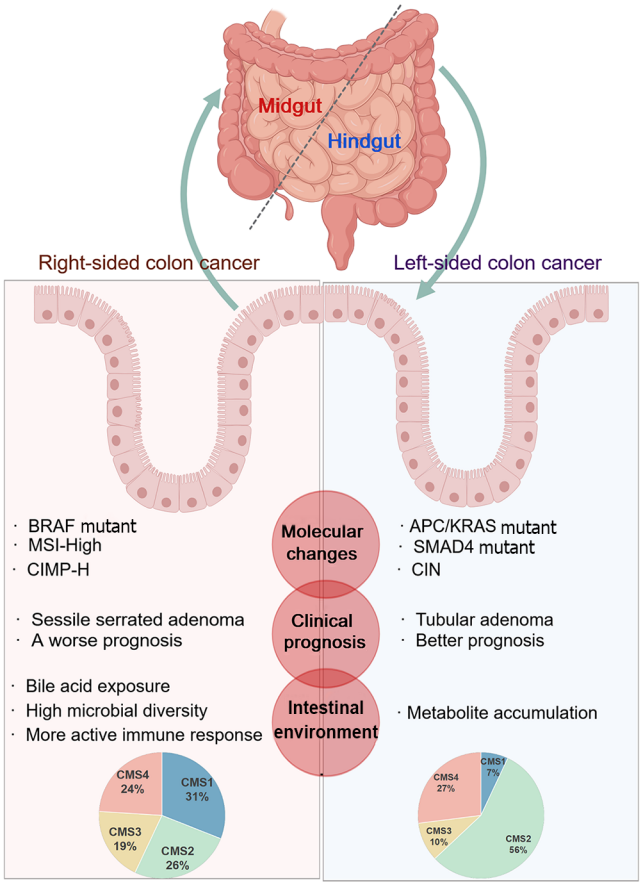

Figure 2 Biological characteristics and molecular distinctions between the left and right - sided colon. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. The figure details the differences in the origin, molecular changes, clinical prognosis, and intestinal environment of the left and right-sided colon cancer. CIN: Chromosomal instability; MSI-H: High Microsatellite instability; CIMP-H: CpG island methylator phenotype-high; CMS: Consensus molecular subtypes; APC: Adenomatous polyposis col; KRAS: Kirsten rat sarcoma viral oncogene homolog; SMAD4: Sma and mad homolog; BRAF: B-Raf proto-oncogene.

iveness, treatment strategies, and overall prognosis[33]. Therefore, it is crucial to evaluate right and left colon cancers as separate entities to develop more effective and personalized treatment approaches.

The right-sided colon (Figure 2) features a larger lumen with a thinner wall, primarily designed for the absorption of water and electrolytes, as well as the storage of feces. It receives digestive fluids, bile acids, and partially digested food from the small intestine. Despite the relatively short exposure time of carcinogens to the intestinal mucosa, there is a potential for increased exposure to carcinogens that are ingested through food. The greater microbial diversity in the right-sided colon can influence the immune microenvironment, promoting tumor cell proliferation, invasion, and metastasis[34,35]. The presence of abundant lymphoid tissue and immune cells leads to a more active immune response, which can affect tumor growth and metastasis. Right-sided colon cancer often manifests as sessile serrated adenomas, which are typically detected at later stages and are characterized by poor differentiation, high cellular atypia, frequent mucinous carcinoma, signet-ring cell carcinoma, undifferentiated carcinoma, and strong invasive and metastatic capabilities[36]. This contributes to the limited efficacy of conventional chemotherapy while showing better responsiveness to immunotherapy. Right-sided colon cancer is also associated with *BRAF* mutations, MLH1 hypermethylation, MSI positivity, and CIMP-H[37].

In contrast, the left colon (Figure 2) is smaller in size, has thicker walls, and exhibits faster peristalsis. It forms and transports more solid feces due to increased water absorption, resulting in a longer fecal residence time[38]. This prolonged retention can lead to the accumulation of potentially carcinogenic bacterial metabolites. Consequently, CIN is more prevalent in this region, associated with the inactivation of TSGs such as *APC*, *P53*, and *SMAD4*, as well as frequent mutations in *KRAS* and *PIK3CA*[39]. Left-sided colon cancer generally exhibits better differentiation compared to its right-sided counterpart, with tumor cell growth being more regular and less aggressive. These tumors often begin as tubular adenomas and progress to infiltrating and sclerotic adenocarcinomas with higher differentiation. Patients with left-sided colon cancer typically benefit from 5-fluorouracil (5-FU)-based adjuvant chemotherapy and targeted therapies, resulting in improved overall survival compared to those with right-sided tumors. Notably, anti-epidermal growth factor receptor (*EGFR*) monoclonal antibody therapies (such as cetuximab and panitumumab) demonstrate significantly better responses in left-sided colon cancer[40].

TRANSCRIPTOMICS-BASED CMS OF CRC

The development of cancer arises from complex interactions among multiple genes. TCGA project in the United States aims to uncover the genomic characteristics of cancer, facilitating advancements in diagnosis and treatment. Initially, prognosis relied on markers such as CIN, MSI, or CIMP. However, CRC exhibits significant histological heterogeneity both between and within patients[41]. Subsequent research utilizing Sanger sequencing identified transcriptome molecular subtypes, some of which displayed consistent features, while others lacked uniformity[42]. In 2015, the CRC Typing Consortium combined six classification systems, resulting in the identification of four CMS: CMS1 (MSI immune), CMS2 (classical), CMS3 (metabolic), and CMS4 (mesenchymal)[10]. Approximately 13% of CRC cases remain unclassified due to intratumoral heterogeneity and are categorized as mixed types. This classification aids in recognizing patient-specific disease characteristics and informing treatment decisions.

Key features of the CMS1

CMS1 (MSI immune) represents about 14% of CRC cases and is predominantly observed in females. It typically arises in the right-sided colon and is associated with higher histopathological differentiation. This subtype is linked to non-specific intestinal symptoms, including diarrhea and mucinous stools[43]. CMS1 is characterized by hypermutation but exhibits CIN-L. It encompasses most cases of MSI-H, CIMP-H, and *BRAF* mutations (Figure 3). Furthermore, it demonstrates increased gene expression related to immune cell infiltration and immune escape[44].

CMS1 displays high immunogenicity and significant immune cell infiltration (Figure 4), making it a candidate for immune checkpoint inhibitor therapy. *MMR* genes tend to accumulate mutations at a higher frequency compared to other genomic regions. As a result, MSI-H tumors exhibit a substantially elevated tumor mutational burden, with mutation levels 100 times to 1000 times greater than those in MSS tumors, which correlates with reduced overall survival in patients with a high tumor mutational burden. These mutations generate numerous neoantigens that activate the immune system, eliciting robust immune responses. CMS1 tumors are enriched with various immune cells, including $CD8^+$ cytotoxic T cells, natural killer cells, dendritic cells, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), tumor-associated macrophages, and B lymphocytes. Elevated levels of cytokines such as C-X-C motif chemokine ligands 9 (*CXCL9*), C-X-C motif chemokine ligands 10 (CXCL10), interferon-γ, and interleukin (IL)-15 enhance local immune activity and improve prognosis[45]. Key signaling pathways, including Janus activated kinase (*JAK*) - signal transducer and activator of transcription (*STAT*) (Figure 5)[46], promote inflammatory responses and the recruitment of immune cells. However, tumor cells can suppress T cell activity through the overexpression of immune checkpoint molecules[47]. Initially, CMS1 typically shows a more favorable prognosis, attributed to a high level of immune cell infiltration. However, the increased frequency of somatic mutations in CMS1 Leads to significant tumor heterogeneity. This heterogeneity facilitates the emergence of more aggressive and treatment-resistant mutations, particularly after therapeutic interventions. As a result, the prognosis for CMS1 worsens significantly following recurrence and metastasis.

In CMS1, *EGFR* activation initiates downstream signaling through the rat sarcoma (*RAS*)-rapidly RAF-mitogen-activated extracellular signal-regulated kinase (*MEK*)–extracellular signal-regulated kinase (*ERK*), mitogen-activated protein kinase (*MAPK*), and *PI3K-AKT*-mechanistic target of rapamycin (mechanistic target of rapamycin) pathways (Figure 5), resulting in cell cycle progression, enhanced DNA synthesis, increased cell survival, and morphological changes. Aberrant *EGFR* signaling is closely associated with cancer development, making targeted therapies against *EGFR* and its downstream components a critical focus in anti-cancer strategies[48]. Understanding these mechanisms could pave the way for novel therapeutic interventions for *EGFR*-mediated diseases. The *BRAF V600E* mutation, which substitutes valine with glutamate at position 600, is the most prevalent *BRAF* mutation in CRC, accounting for approximately 90% of all *BRAF* mutations[49]. This mutation leads to sustained activation of *MAPK* signaling, particularly through the *RAS-RAF-MEK-ERK* pathway, promoting tumor proliferation and metastasis[50]. In CMS1, the PIK3CA pathway is aberrantly activated due to gene mutations, resulting in *PI3K* activation, which catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol (3,4,5)-trisphosphate, subsequently activating AKT and *mTOR*. This promotes cell proliferation, survival, and metabolic reprogramming to support rapid cell growth. The activation of the *PI3K/AKT/mTOR* pathway in CMS1 encourages the secretion of immunosuppressive factors by tumor cells, undermining antitumor immune responses and creating an unfavorable microenvironment. Despite *EGFR* activation in CMS1 CRC, treatment strategies prioritize immunotherapy over traditional targeted therapies due to complex genetics and diverse resistance mechanisms[51].

In CMS1, CIMP-H plays a significant role in tumor biology[52]. CIMP-H induces hypermethylation in gene promoter regions, silencing essential genes such as tumor suppressors and *MMR* genes, which leads to MSI-H[53]. This enhances the expression of immune-related genes, increasing immune cell infiltration and the expression of immune checkpoint genes, making CMS1 more responsive to immunotherapy. CIMP-H frequently co-occurs with *BRAF* mutations, activating the *MAPK* pathway and promoting tumor proliferation and survival.

Key features of the CMS2

CMS2 (canonical) accounts for approximately 37% of CRC cases and is the most prevalent CMS subtype, characterized by a broad range of onset ages and frequent localization in the left-sided colon and rectum[54]. It follows the adenoma-carcinoma progression sequence. Patients with CMS2 generally respond well to standard treatments and have a moderate to favorable prognosis, with high survival rates even after recurrence. Key biological characteristics include CIN, SCNA, elevated *P53* mutation rates, and a CIMP-L rate (Figure 3)[55].

The CMS2 subtype is marked by an immunosuppressive microenvironment with limited immune cell infiltration (Figure 4)[44]. Tumor cells suppress T cell activity through cytokines such as *TGF-β*, IL-10, and IL-6, with stromal cells

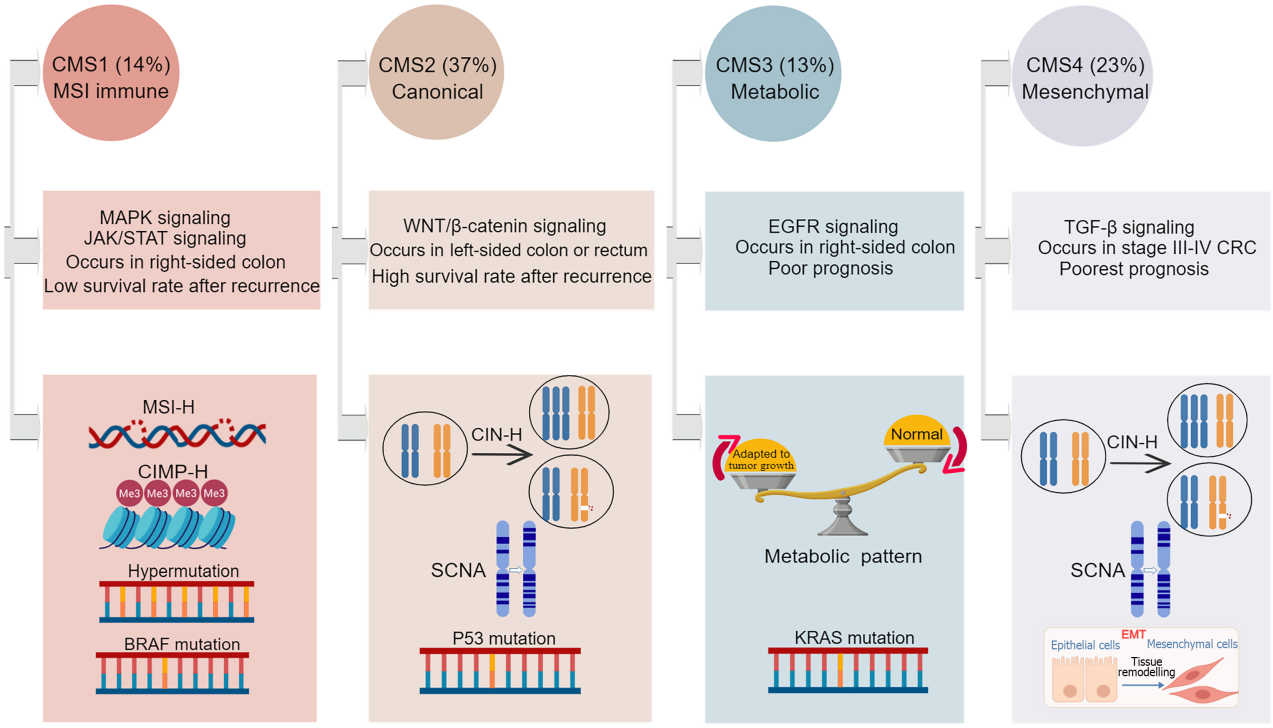

Figure 3 Key features of the four consensus molecular subtypes. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. CRC: Colorectal cancer; CMS: Consensus molecular subtypes; CIN-H: High-level chromosome instability; CIMP-H: CpG island methylator phenotype-high; MSI-H: High microsatellite instability; SCNA: Somatic copy number alteration; EMT: Epithelial-mesenchymal transition; TGF-β: Transforming growth factor beta; MAPK: Mitogen-activated protein kinase; STAT: Signal transducer and activator of transcription; EGFR: Epidermal growth factor receptor; JAK: Janus kinase.

also contributing to this immune suppression. Immune cells are largely excluded from the tumor core, with only a few MDSC and Tregs present. This exclusion may result from abnormal molecular expression on tumor cells or altered extracellular matrix components. Additionally, low neoantigen production further restricts the immune response[56].

Activation of the *Wnt/β-catenin* pathway (Figure 5) in CMS2 typically arises from mutations in the *APC* gene or the nuclear accumulation of *β-catenin*[57]. The *Wnt* ligand binds to its frizzled receptor, leading to the inactivation of glycogen synthase kinase 3 beta. Mutated *APC* allows *β-catenin* to evade degradation, accumulate, and translocate into the nucleus, where it interacts with lymphoid enhancer-binding factor/T-cell factor (*TCF*) transcription factors to activate target genes such as the myelocytomatosis oncogene (*MYC*) proto-oncogene and *cyclin D1*[58]. These genes promote cell proliferation, inhibit apoptosis, and maintain stem cell characteristics. Notably, overexpression of *MYC* can induce "*MYC* addiction", making certain tumor cells highly reliant on *MYC* for survival, which provides a rationale for therapeutic targeting[59]. Aberrant activation of the *Wnt/β-catenin* pathway drives the transformation from adenoma to carcinoma and may contribute to the formation of tumor-initiating cell populations, which are potential sources of relapse and drug resistance [60]. Approximately 80% of *APC* mutations, one of the earliest genetic alterations in colorectal carcinogenesis, lead to increased nuclear *β-catenin* levels[61]. This results in the formation of the *TCF/β-catenin* complex, inhibiting epithelial differentiation and promoting tumorigenesis[62]. In CMS2, mutations in *PIK3CA* are common. These mutations in the p110α subunit of *PI3K* can aberrantly activate the *PI3K-Akt-mTOR* signaling pathway, leading to abnormal cell cycle progression, reduced cellular adhesion, decreased apoptosis, and angiogenesis, thereby facilitating tumor initiation and progression[63].

CMS2 tumors are frequently associated with CIN, resulting in abnormal chromosome numbers and structural aberrations due to mutations in key genes such as *P53* and *SMAD4*[64]. Inactivated *P53* impairs the DNA damage response, leading to CIN and increased genomic heterogeneity. CIN also enhances genetic variation within the tumor, affecting drug sensitivities and treatment efficacy. Understanding the role of CIN in CMS2 is crucial for predicting disease progression and developing personalized treatments. CMS2 tumors exhibit high proliferative activity; loss of *TP53* disrupts the balance between proliferation and apoptosis, promoting abnormal cell growth. *TP53* mutations are linked to lymphatic and vascular invasion, enhancing invasive and metastatic capabilities[65]. CRC patients with mutant *P53* demonstrate higher resistance to chemotherapy and poorer prognosis, which likely applies to CMS2 as well[66]. Reactivating *TP53* function shows promise as a therapeutic strategy, with encouraging results observed in cell lines and animal models. Furthermore, CIN manifests as SCNA, increasing genomic instability and enhancing tumor adaptability to environmental changes, impacting disease progression and treatment response.

Key features of the CMS3

CMS3 (metabolic) accounts for about 13% of CRC cases. This subtype primarily affects middle-aged patients in the right-sided colon. Most cases progress from adenoma to carcinoma, exhibiting localized invasive behavior with lower rates of

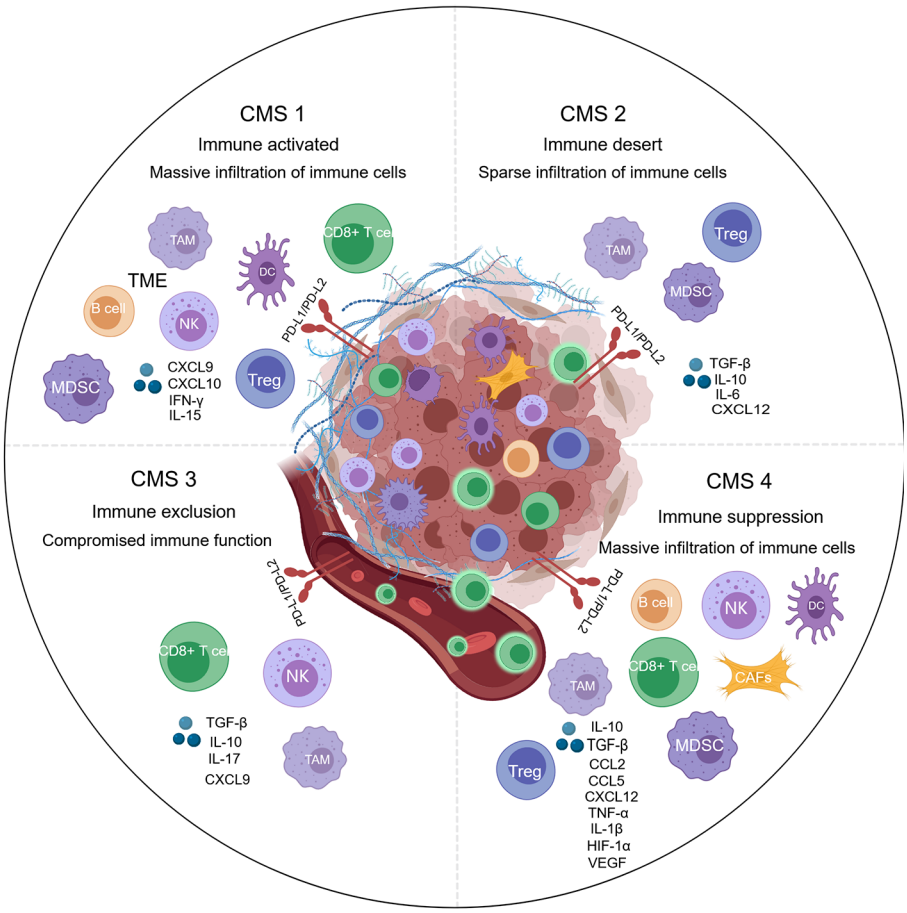

Figure 4 The distinct immune landscapes of the tumor microenvironments across the four consensus molecular subtypes of colorectal cancer. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. Consensus molecular subtypes (CMS) 1 is characterized by an "immune activated" environment with massive immune cells. CMS2 is an "immune desert" with sparse infiltration of immune cells. CMS3 is called "immune exclusion", in which immune cells compromised are present and located on the periphery of the tumor nest. CMS4 exhibits "immune suppression", even with an abundance of immune cells. CRC: Colorectal cancer; CMS: Consensus molecular subtypes; DC: Dendritic cells; MDSC: Myeloid-derived suppressor cell; TAM: Tumor-associated macrophages; EMT: Epithelial-mesenchymal transition; PD-L1: Programmed death-ligand 1; PD-L2: Programmed death-ligand 2; IL: Interleukin; TGF-β: Transforming growth factor beta; TME: Tumor microenvironment ; NK: Natural killer; CXCL: C-X-C chemokine ligand; IFN: Interferon; CCL: Chemokine (C-C motif) ligand; HIF-1α: Hypoxia-inducible factor-1α; VEGF: Vascular endothelial growth factor.

lymph node metastasis and poorer overall survival. CMS3 shows fewer instances of CIN, a higher prevalence of CIMP (primarily CIMP-L), and approximately 30% of cases exhibit high mutation rates, enriched with *KRAS* mutations (Figure 3)[67].

The CMS3 subtype is characterized by impaired immune function, reduced immune cell infiltration, and increased levels of immunosuppressive factors (Figure 4)[44]. The metabolic reprogramming of tumor cells leads to immune cell dysfunction, such as inhibiting T-cell activity by consuming glucose and amino acids. Although CMS3 tumors generally show lower levels of immune cell infiltration, small populations of Tregs and MDSCs may still be present in the tumor microenvironment in certain instances. However, the functionality of these immune cells is often compromised, partly due to diminished antigen presentation on tumor cell surfaces or increased expression of immune checkpoint molecules such as programmed death-ligand 1 (*PD-L1*). Additionally, CMS3 tumors secrete various immunosuppressive factors, including IL-10, *TGF-β*, and IL-17, which weaken the host immune system's ability to combat cancer. These factors not only directly inhibit immune cell activity but also promote the proliferation of immunosuppressive cells, such as Tregs and MDSCs, leading to their accumulation within the tumor microenvironment. This creates an environment that is unfavorable for effective anti-tumor immune responses, further suppressing immune reactions[68].

In the intestinal mucosal epithelium, normal cells initially undergo a series of genetic changes, such as the inactivation of the *APC* gene, which is a crucial early event that leads to uncontrolled cell proliferation and the development of adenomas. Over time, additional genetic mutations, including *KRAS* mutations, gradually convert the adenoma into cancer. During this transformation, the metabolic profile undergoes remodeling, shifting from normal metabolic patterns to a tumor-adaptive metabolic phenotype. The most common alteration in CMS3 tumors is an activating *KRAS* mutation, which results in the persistent activation of the *RAS/RAF/MEK/ERK* signaling pathway (Figure 5)[69,70]. *KRAS*, a small guanosine-triphosphate hydrolase, activates a series of downstream effectors, including members of the *RAF* kinase family (*e.g.*, *BRAF*)[71], which subsequently activate *MEK* and *ERK* kinases. This activated pathway also drives metabolic reprogramming to meet the energy demands of rapid cell proliferation. For instance, it enhances glycolysis by regulating key enzymes such as glucose transporters and hexokinases, while simultaneously optimizing oxidative phosphorylation

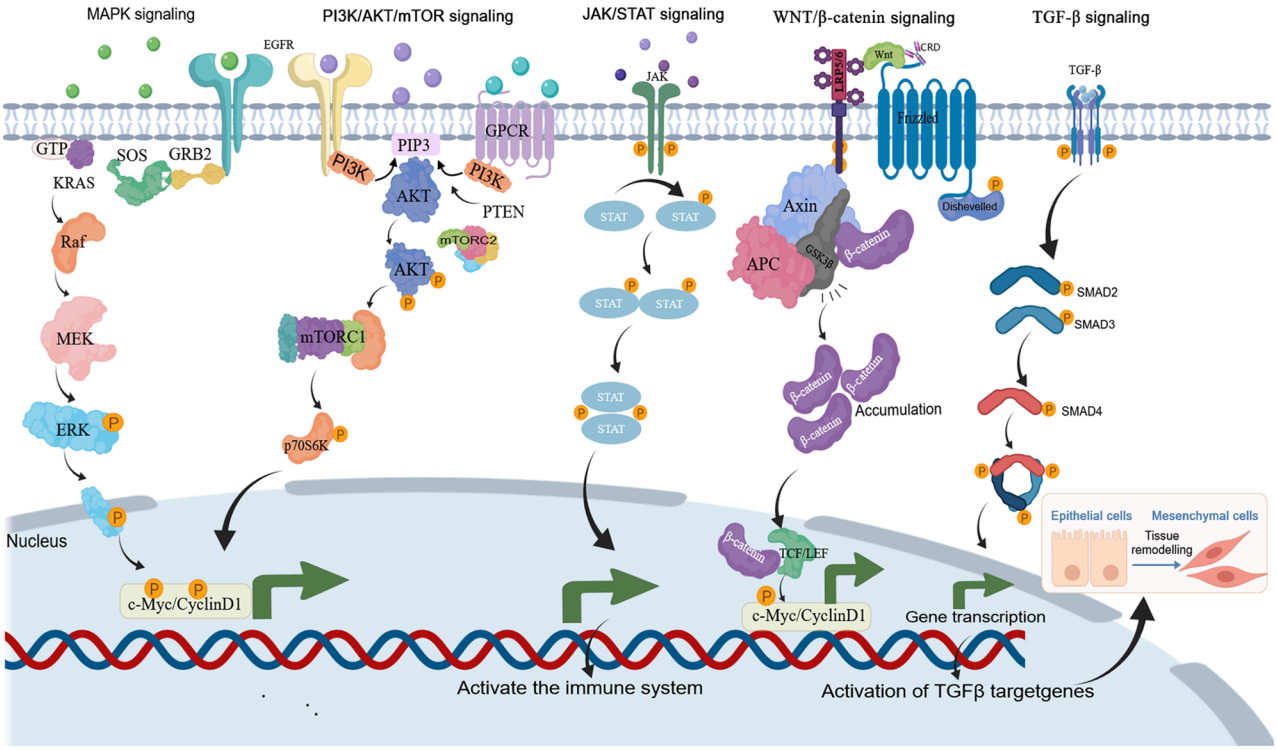

Figure 5 Key signaling pathways in colorectal cancer such as mitogen-activated protein kinase signaling, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin signaling, Janus kinase/signal transducer and activator of transcription signaling, Wnt/β-catenin signaling, transforming growth factor beta signaling. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mechanistic target of rapamycin; JAK: Janus activated kinase; STAT: Signal transducer and activator of transcription; TGF-β: Transforming growth factor beta; SMAD: Sma and mad homolog; GPT: Guanosine Triphosphate; SOS: Son of sevenless; GRB2: Growth factor receptor-bound protein 2; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase; AKT: Protein kinase B; PI3K: Phosphatidylinositol 3-kinase; PIP3: Phosphatidylinositol 3,4,5-trisphosphate; TCF: T-cell factor; LEF: Lymphoid enhancer-binding factor; EMT: Epithelial-mesenchymal transition.

by modulating mitochondrial function and fatty acid synthesis to ensure sufficient ATP production[72]. In addition to glycolysis, glutamine metabolism plays a significant role in CMS3. Glutamine, an amino acid and nitrogen source, is widely utilized for synthesizing nucleotides and proteins, and provides fuel for mitochondria through the tricarboxylic acid cycle. CMS3 tumor cells also enhance fatty acid synthesis to meet the demands of membrane structure renewal and signal transduction. At the same time, they maintain a certain level of fatty acid β-oxidation to balance energy needs and provide an additional energy source when required. Furthermore, the PI3K-*AKT*-*mTOR* pathway is central to regulating cell survival, migration, and angiogenesis[73] (Figure 5). In CMS3, *PI3K* catalyzes the production of phosphatidylinositol (3,4,5)-trisphosphate, which subsequently recruits and activates *AKT*. *AKT* then phosphorylates multiple substrates, including Raptor, a key component of the *mTORC1* complex, ultimately leading to the activation of *mTORC1*. *mTORC1* further regulates translation initiation factors, ribosome biogenesis, and other proteins related to cell growth while inhibiting autophagy to ensure an adequate supply of nutrients to sustain rapid tumor proliferation[74].

Key features of the CMS4

CMS4 (mesenchymal) accounts for approximately 23% of CRC cases. The age of onset is relatively younger, with tumors often diagnosed at later stages, commonly in stages III and IV, and a higher proportion of rectal cancer. Overall survival and recurrence-free survival rates are lower, making it the subtype with the poorest prognosis. This type of cancer is frequently associated with significant invasiveness and metastatic potential, particularly to the liver. This often necessitates more aggressive and comprehensive treatment approaches, including a combination of surgery, chemoradiotherapy, and novel targeted therapies to manage the disease. CMS4 is characterized by a high frequency of CIN, a high mutation rate of *P53*, and a low CIMP rate. It features epithelial-mesenchymal transition (EMT), upregulation of *TGF-β*, stromal infiltration, and angiogenesis as major traits (Figure 3). The tumor microenvironment is notably enriched in CAFs and immune cells[75].

The CMS4 subtype is marked by significant immune cell infiltration and an immunosuppressive microenvironment (Figure 4). CMS4 tumors are rich in various immune cell types, including $CD8^+$ T cells, natural killer cells, and TAM. However, the functionality of these immune cells is often suppressed, partly due to reduced antigen presentation on the surface of tumor cells or increased expression of immune checkpoint molecules such as *PD-L1*[76]. CAFs play a crucial role in modifying the tumor microenvironment by releasing cytokines and chemokines, which further suppress immune responses. For example, CMS4 tumors can diminish the host immune system's ability to combat cancer by producing

various immunosuppressive factors, such as *TGF-β* and IL-10, which assist the tumor in escaping immune detection. These factors not only inhibit immune cell function directly but also encourage the buildup of immunosuppressive cell types, including Treg and MDSC, thereby creating an environment that is detrimental to antitumor immune responses [77].

Within the CMS4 tumor microenvironment, CAFs release extracellular matrix components like collagen and fibronectin, along with growth factors such as platelet-derived growth factor, which alter the physical barriers surrounding the tumor. Additionally, CAFs facilitate angiogenesis by secreting vascular endothelial growth factor (*VEGF*) and other pro-angiogenic substances, ensuring the tumor receives adequate oxygen and nutrients. The *TGF-β* signaling pathway (Figure 5) governs various processes, including cell proliferation, differentiation, migration, and adhesion. When *TGF-β* binds to its receptors, it triggers receptor dimerization, forming a complex that activates signaling pathways. This process activates kinase domains that phosphorylate and activate *SMAD2/3* proteins, which then combine with *SMAD4* and move to the nucleus to regulate *TGF-β* target genes[78]. In advanced stages of CRC, elevated *TGF-β* expression leads to EMT. Consequently, increased invasion and cell migration result in diminished immune responses from normal cells. Moreover, the interaction between CAFs and tumor cells can amplify *TGF-β* signaling, prompting CAFs to secrete additional cytokines, thus perpetuating a harmful cycle. The EMT process enhances the migratory and invasive capabilities of tumor cells, facilitating metastasis to distant organs[79]. This process not only boosts migratory ability and invasiveness but also raises the risk of recurrence. Furthermore, the NOTCH pathway intensifies metastatic potential by promoting EMT and neutrophil infiltration[80]. Thus, CMS4 relies not only on inherent genetic changes but also on the contributions of CAFs and immune cells within the tumor microenvironment.

CIN is prevalent in CMS4 and significantly impacts tumor initiation and progression through various mechanisms. It primarily arises from critical gene mutations, including *P53* inactivation, *BUB1B*/*BUBR1*, and *AURKA*, which disrupt the cellular response to DNA damage and the proper distribution of chromosomes, leading to increased genomic heterogeneity[81]. The substantial genetic diversity resulting from CIN enhances the aggressiveness and metastatic potential of CMS4 tumors while facilitating stromal remodeling and EMT, which in turn promotes tumor cell migration and overall malignancy. Additionally, CIN modifies energy metabolism to meet the energy requirements of rapid cell proliferation and may create a microenvironment that is less favorable to anti-tumor immune responses through the generation of neoantigens and the release of immunosuppressive factors. Given the pivotal role of CIN in CMS4, developing therapeutic strategies that target CIN - such as stabilizing microtubules, enhancing spindle assembly checkpoint function, or combining with immunotherapy - has become a significant focus for future research. Accurately identifying and intervening in CIN-related molecular events holds promise for improving clinical outcomes for patients with CMS4.

IMMUNOTHERAPY FOR CRC

Immune checkpoint inhibitor therapy has revolutionized the treatment landscape for various solid tumors, demonstrating the potential for prolonged remission in patients with advanced metastatic disease who have undergone extensive prior therapies[82,83]. The CMS1 subtype is characterized by MSI-H and MMR deficiency (dMMR), showing exceptional responsiveness to immunotherapy. The landmark KEYNOTE-016 trial in 2015 first identified MSI-H/dMMR as a critical biomarker for assessing the effectiveness of immunotherapy, paving the way for future therapeutic advancements. In 2017, the Food and Drug Administration approved pembrolizumab and nivolumab, two anti-programmed cell death protein 1 (*PD-1*) monoclonal antibodies, for treating MSI-H/dMMR metastatic CRC. The pivotal phase III KEYNOTE-177 trial enrolled 307 patients with untreated metastatic MSI-H/dMMR CRC, randomly assigning them in a 1:1 ratio to receive either pembrolizumab or chemotherapy. With a median follow-up of 32.4 months, pembrolizumab showed a significant improvement in progression-free survival (16.5 months compared to 8.2 months). Notably, among patients achieving overall remission, 83% in the pembrolizumab group remained in remission at 24 months, in contrast to only 35% in the chemotherapy group[84,85]. This finding firmly establishes immunotherapy as the standard first-line treatment for MSI-H/dMMR CRC, including for patients who have previously been treated with 5-FU, oxaliplatin, and irinotecan.

Another significant mechanism of immunotherapy focuses on the interaction between *PD-1* and *PD-L1*. Elevated levels of *PD-L1* on tumor cells can serve as a predictive biomarker, suggesting that the tumor has established methods to evade immune responses. Tumors exhibiting high *PD-L1* expression tend to be more aggressive and associated with a poorer prognosis, yet they may also show increased sensitivity to immune checkpoint inhibitor therapies. Immunotherapeutic agents, such as pembrolizumab and nivolumab, which inhibit the *PD-1/PD-L1* interaction, have demonstrated effectiveness in certain *PD-L1*-positive CRC patients. Furthermore, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another crucial immune checkpoint marker in CRC[86]. Similarly, elevated CTLA-4 expression correlates with immune evasion and a worse prognosis, prompting the evaluation of CTLA-4-targeting therapies in clinical trials for their potential advantages. Lenz *et al*[87] reported the effectiveness of nivolumab (an anti-*PD-1* monoclonal antibody) combined with low-dose ipilimumab (an anti-CTLA-4 monoclonal antibody) as a first-line treatment for patients with metastatic MSI-H/dMMR CRC. The study found that this combination therapy achieved an objective response rate (ORR) of 69% and a disease control rate of 84% in untreated MSI-H/dMMR patients. Additionally, a higher presence of activated cytotoxic T cells within tumor-infiltrating lymphocytes often indicates a more favorable prognosis and suggests that the tumor may be more responsive to immune-based therapeutic strategies[88].

Immunotherapy for CRC has shown impressive efficacy in treating dMMR or MSI-H cancers, particularly with *PD-1*/*PD-L1* inhibitors providing long-lasting disease control for some patients. Checkpoint inhibitors enhance survival rates, and combination therapies exhibit promise. However, only about 5% of patients experience benefits, with poor outcomes

in MSS or dMMR cases, alongside immune-related adverse effects and tumor heterogeneity impacting efficacy. Challenges include accurate biomarker screening, treatment optimization, personalized care, accessibility to genomic analysis, and the exploration of combination strategies. Future research aims to identify new biomarkers, investigate synergies with other treatments, and address resistance mechanisms. Technological advancements and cost reductions are anticipated to make immunotherapy more accessible, providing effective personalized treatment to a larger patient population, ultimately improving outcomes, quality of life, and survival rates.

METABOLIC INHIBITORS FOR CRC

In recent years, the use of metabolic inhibitors in CRC treatment has garnered increasing interest. Currently, metabolic inhibitors like the glutaminase inhibitor CB-839 have shown significant antitumor effects in various studies. The CMS3 subtype is marked by considerable metabolic reprogramming, including the upregulation of the glutamine pathway, which is closely linked to *KRAS* mutations[89]. Research indicates that inhibiting specific amino acid transporters, such as amino acid transporter LAT1, can effectively reverse the hyperproliferative phenotype induced by *KRAS* activation, delay adenoma formation, and enhance sensitivity to *mTORC1* inhibitors. Zhao *et al*[90] found that CB-839, when used in conjunction with 5-FU, effectively inhibits the growth of PIK3CA-mutated CRC and induces tumor regression. Treatment with CB-839 increases the conversion of 5-FU to its active metabolite 5-fluoro-2′-deoxyuridine monophosphate by upregulating the expression of uridine phosphorylase 1, thereby intensifying the inhibition of thymidylate synthase by 5-FU. The study also reported that the combination of CB-839 and capecitabine (a prodrug of 5-FU) was well-tolerated in a phase I clinical trial and showed potential clinical benefits for patients with PIK3CA-mutated CRC. This suggests that targeting glutamine metabolism may represent an effective strategy for treating PIK3CA-mutated CRC and warrants further clinical investigation.

TARGETED THERAPY OF CRC

Targeted drugs for BRAF mutations

In the CMS1 subtype of CRC, the frequent presence of *BRAF* mutations, along with distinct characteristics of the tumor microenvironment, leads to unique biological behaviors and therapeutic challenges. Targeted therapies for *BRAF V600E* mutations primarily involve *BRAF* inhibitors and *MEK* inhibitors. Monotherapy with *BRAF* inhibitors has limited effectiveness; thus, combination therapy is necessary to overcome resistance. Clinical trials often combine *BRAF* inhibitors with *EGFR* inhibitors to achieve better outcomes[91]. The BEACON CRC phase III trial demonstrated that the triplet combination of encorafenib (a *BRAF* inhibitor), binimetinib (a *MEK* inhibitor), and cetuximab (an *EGFR* inhibitor), along with the doublet combination of encorafenib and cetuximab, significantly enhanced overall survival and response rates compared to standard treatments (encorafenib combined with irinotecan or FOLFIRI irinotecan, leucovorin, fluorouracil]) [92]. These results present new strategies for managing *BRAF V600E*-mutated CRC, particularly in the poor-prognosis CMS1 subtype. The SWOG S1406 study evaluated irinotecan and cetuximab with or without vemurafenib (a *BRAF* inhibitor) in patients with *BRAF*-mutated metastatic CRC. The findings indicated notable improvements in progression-free survival and ORRs with the addition of vemurafenib[93]. This suggests that combining vemurafenib with irinotecan and cetuximab may provide significant clinical advantages for CRC patients with the *BRAF* V600E mutation, extending this therapeutic benefit beyond the CMS1 subtype. A phase II trial (NCT03668431) investigated the combination of spartalizumab (a *PD-1* inhibitor), dabrafenib (a *BRAF* inhibitor), and trametinib (a *MEK* inhibitor). This combination achieved an ORR of 24.3% in patients with *BRAF V600E*-mutated CRC, surpassing control data[94]. Additionally, single-cell RNA sequencing analysis revealed that patients with favorable therapeutic responses exhibited enhanced activation of intrinsic immune programs within tumor cells and more comprehensive *MAPK* pathway inhibition. The integration of targeted therapy with chemotherapy or immunotherapy not only curtails tumor proliferation but also improves prognosis by bolstering immune responses, paving the way for new avenues in precision therapy. *BRAF*-targeted agents have shown effectiveness in CRC treatment, enhancing both progression-free survival and overall survival. However, challenges persist, including limited efficacy of monotherapy, restricted response rates, resistance issues, and uncertainty regarding the selection of combination therapies. Future advancements in understanding the mechanisms of *BRAF* mutations, developing novel targeted agents, and optimizing combination therapies may improve the effectiveness and applicability of *BRAF*-targeted treatments in CRC.

Targeted drugs for Wnt pathway

The *Wnt/β-catenin* signaling pathway is crucial in CRC, particularly in the CMS2 subtype. Research has investigated targeting this pathway as a therapeutic approach. Porcupine inhibitors, including LGK974, ETC159, and RXC004, inhibit *Wnt* activation by blocking the palmitoylation of *Wnt* ligands, thereby reducing cell proliferation and migration[95]. Approximately 80% of CRC cases display *APC* mutations, leading to abnormal *Wnt* activation, making Porcupine a significant target. SM08502 inhibits CDC-like kinase activity, disrupts spliceosome function, and decreases *Wnt*-related gene expression, demonstrating antitumor effects in gastrointestinal cancer models[96]. NU2058, a ran binding protein 3 inhibitor, selectively inhibits *β-catenin* nuclear translocation and induces senescence in CRC cells with nuclear *β-catenin* activation, effectively suppressing tumor growth in preclinical models. The combination of NU2058 with chemotherapeutic agents like oxaliplatin and irinotecan may enhance antitumor activity[97]. Xiang *et al*[98] identified adavivint a

small-molecule inhibitor that disrupts Zn^{2+} dependent a disintegrin and metalloproteinases 10/*NOTCH2/TCF7 L2* signaling independently of the canonical *Wnt/β-catenin* pathway, effectively suppressing CRC growth in both *in vitro* and *in vivo* models[98]. This highlights the Zn^{2+} dependent a disintegrin and metalloproteinases 10/NOTCH2 axis as a potential therapeutic target. Wu *et al*[99] conducted a detailed analysis of ovo-like zinc finger 2, emphasizing its vital role in regulating stem cell properties and immune cell infiltration, providing new insights into the *Wnt* pathway's role in various cancers[99]. Ovo-like zinc finger 2's regulatory effects on the *Wnt* signaling pathway and its influence on the tumor microenvironment offer potential strategies for targeting the CMS2 subtype of CRC. The *Wnt* signaling pathway is abnormally activated in most CRC cases. Drugs targeting the *Wnt* pathway can inhibit cancer cell growth, with some clinical trials demonstrating tumor reduction and decreased biomarkers. However, challenges include the complexity of the pathway, difficulties in precise inhibition, drug resistance, and a lack of predictive biomarkers. Advanced genomic analysis, high research and development costs, optimized dosing strategies, and clear treatment guidelines are essential. Future efforts may focus on developing precise inhibitors, exploring combination therapies, and identifying effective biomarkers to enhance treatment efficacy and scope.

Targeted drugs for MYC

MYC activation in CRC is influenced by signaling pathways such as *Wnt/β-catenin*, *MAPK*, and *PI3K/AKT/mTOR*, rather than through gene rearrangements or amplifications. This leads to increased *MYC* protein levels, which in turn promotes cancer progression and resistance to treatment. In the CMS2 subtype, the abnormal activation of these pathways is prevalent, making *MYC* a compelling therapeutic target[100]. Considerable advancements have been made in the development of targeted therapies against *MYC*, including MYC-associated factor X inhibitors (SaJM589, MYCi975) that inhibit MYC-dependent transcription; Pin1 inhibitors (such as KPT-6566, developed by Karyopharm Therapeutics) that facilitate *MYC* degradation; and Pim1 inhibitors (such as AZD1208, developed by AstraZeneca Development) that obstruct *MYC*-related oncogenic transcription[101]. Although complete remission has not been achieved in patients, the stabilization of disease progression and the inhibition of *MYC* target gene expression by omomyc-103 suggest potential benefits for CRC patients with ongoing *MYC* activation[102]. Despite the promise of these drugs, their lack of specificity for *MYC* presents a challenge. Further investigation into the underlying mechanisms, suitable patient populations, and combination therapies within the CMS2 subtype is essential for developing more precise and effective treatments, potentially paving the way for new strategies in managing this CRC subtype.

Targeted drugs for KRAS

Historically, *KRAS* has been viewed as an undruggable target; however, recent research has begun to challenge this notion. *KRAS* mutations, particularly at positions G12 and G13, are prevalent drivers in CRC, especially within the CMS3 subtype. These mutations lead to the overactivation of downstream signaling pathways, contributing to tumor initiation and progression. Consequently, the development of specific *KRAS* inhibitors has emerged as a crucial strategy for treating this cancer type[103]. Recent advancements have made significant strides in targeting *KRAS*, both directly and indirectly. Sotorasib (AMG 510), the first *KRAS G12C* inhibitor approved for non-small cell lung cancer, provides insights for treating other malignancies. The *KRAS G12D* mutation involves the substitution of glycine at position 12 with aspartic acid. Unlike G12C, the carboxyl group of G12D has weak nucleophilicity under physiological conditions, necessitating the introduction of basic groups to form a salt bridge with G12D for effective binding. MRTX1133 is the first reported *KRAS* G12D inhibitor, which forms a salt bridge with D12 and occupies the S-II pocket, demonstrating high affinity[104, 105]. Pan-*KRAS* inhibitors aim to target all *KRAS* mutants, with BI-2852 targeting the S-I/S-II pocket to inhibit both KRAS-guanosine triphosphate and *KRAS*-guanosine diphosphate[106]. The development of these inhibitors offers new strategies for addressing various KRAS mutations, showcasing the potential for directly targeting *KRAS* and inspiring further research to overcome resistance challenges. While *KRAS*-targeted drugs have shown efficacy in CRC, they face obstacles such as limited mutation types (affecting only 3%-4% of patients), resistance (including secondary *KRAS* mutations and bypass activation), and toxicity (with a 27.7% incidence of grade 3-4 adverse reactions). Additional challenges include low rates of biomarker testing, optimizing combination therapies, and managing long-term outcomes. Future strategies may focus on developing broad-spectrum inhibitors (targeting G12D and G13D mutations), exploring new combinations (such as immunotherapy), enhancing patient stratification, and improving drug accessibility to refine precision treatment and prognosis.

Directly targeting *KRAS* is precise but challenging, due to the protein's characteristics and the intratumoral heterogeneity present in CRC. Therefore, indirect strategies, such as inhibiting downstream pathways, enhancing immunotherapy, and modulating the immunosuppressive microenvironment, are necessary. *KRAS* mutations primarily drive tumor growth by activating the *MAPK* pathway. *MEK* inhibitors like Trametinib have shown promise in preclinical studies by inhibiting the proliferation and migration of CRC cells with *KRAS* mutations[107]. Additionally, *KRAS* mutations activate the *PI3K-AKT-mTOR* pathway. *mTOR* inhibitors like everolimus and *AKT* inhibitors like capivasertib have demonstrated antitumor activity in both preclinical and clinical studies[108]. Significant progress has been made in developing *PI3K*-targeted therapies for CRC, including *PI3K* inhibitors such as Alpelisib and dual inhibitors like Omipalisib Research on *KRAS* G12C inhibitors is focusing on immune checkpoints such as *PD-1*, lymphocyte activation gene 3, CTLA-4, T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains, B and T lymphocyte attenuator, T cell immunoglobulin and mucin domain-3, CD73, indoleamine 2,3-dioxygenase 1, and adenosine A2A receptor[109-111]. These molecules play a significant role in promoting immunosuppression within the tumor microenvironment. *KRAS G12C* inhibitors may lower the expression of these checkpoint molecules, thereby altering cytokine levels, metabolic states, and the composition of immune cells to enhance T-cell activation and boost antitumor immune responses.

In the treatment of CRC, tumor vaccines that target *KRAS* mutation-related antigens have emerged as a key area of research. *KRAS* mutations are prevalent in CRC and are closely associated with tumor aggressiveness and immune evasion. Recent studies have employed vaccine strategies to stimulate the immune system to recognize and attack tumor cells that express *KRAS* mutation-related antigens[112]. For example, DNA methyltransferase inhibitors can induce tumor cells to express cancer testis antigens, which can be combined with granulocyte-macrophage colony-stimulating factor gene-transfected tumor cell vaccine (GVAX) vaccines for treatment, demonstrating enhanced antitumor effects in mouse models[113]. Additionally, a clinical trial investigated the combination of GVAX vaccines with the *PD-1* inhibitor pembrolizumab in patients with MMR advanced CRC. Although the primary endpoint of objective response was not achieved, some patients exhibited biochemical responses, indicating that GVAX vaccines might enhance the efficacy of *PD-1* inhibitors by modulating the tumor immune microenvironment[114]. These findings provide initial evidence for *KRAS*-targeted tumor vaccines in CRC, but further clinical trials are necessary to confirm their efficacy and safety. The combination of *KRAS*-targeted therapies, immunotherapies, and tumor vaccines presents new avenues for treating *KRAS*-mutated CRC. While these therapies have demonstrated antitumor activity in clinical trials, additional research is needed to validate their safety and effectiveness. Their integration may become a crucial strategy for managing *KRAS*-mutated CRC in the future.

Targeted drugs for TGF-β pathway

The *TGF-β* signaling pathway is essential for regulating cell proliferation, apoptosis, migration, and EMT, particularly in the CMS4 subtype of CRC. Researchers have developed small-molecule inhibitors, monoclonal antibodies, and other biologics to inhibit *TGF-β* signaling, aiming to counteract effects such as immune evasion, EMT, and angiogenesis[115]. Studies indicate that combining *TGF-β* receptor I inhibitors like galunisertib with neoadjuvant chemoradiotherapy enhances the complete response rate in locally advanced rectal cancer[116]. The bispecific antibody SHR-1701, which targets both *PD-L1* and *TGF-β*, has shown synergistic effects in first-line treatment for unresectable metastatic CRC by boosting antitumor immune responses[117]. Gulley *et al*[118] investigated the dual inhibition of *TGF-β* and *PD-L1*, noting that TGF-β promotes the production of CAFs and immune evasion. This strategy holds promise for treating CRC, particularly in the CMS4 subtype. Niu *et al*[119] developed a novel anti-*TGF-β*/*VEGF* bispecific antibody, Y332D, which inhibits both *TGF-β* and *VEGF* signaling pathways. When combined with *PD-1* inhibitors, Y332D demonstrated significant synergistic antitumor effects in various mouse models[119]. These findings suggest that targeting *TGF-β* could help overcome resistance to immunotherapy and provide new strategies for treating CMS4 CRC.

Targeted drugs for EMT

EMT plays a vital role in the CMS4 subtype of CRC, contributing to tumor metastasis, drug resistance, and immune evasion[120]. EMT is primarily regulated through signaling pathways such as *TGF-β*, *Wnt/β-catenin*, and Notch, which promote tumor cell migration, invasion, and resistance. Significant advancements have been made in developing drugs that target EMT, including *TGF-β* inhibitors, *Wnt/β-catenin* inhibitors, and netrin-1 blockers[121]. However, challenges persist in clinical applications, such as drug specificity, safety, tumor heterogeneity, and the optimization of combination therapy strategies. Future research should focus on developing biomarkers related to EMT to enable personalized treatment, exploring multi-targeted combination therapy strategies to address tumor heterogeneity and drug resistance, and creating novel drugs to further enhance therapeutic efficacy. By gaining a deeper understanding of the mechanisms underlying EMT and refining targeted therapeutic strategies, it is anticipated that these efforts will significantly improve treatment outcomes for CMS4 CRC.

Targeted drugs for VEGF

Angiogenesis is crucial for supplying nutrients and oxygen to growing tumors, making it a vital target in CRC treatment [122]. *VEGF* is the primary driver of angiogenesis and is frequently overexpressed in CRC. The binding of *VEGF* to its receptors initiates processes that lead to the formation of new blood vessels, thereby promoting tumor growth and metastasis. Anti-angiogenic therapies primarily focus on targeting *VEGF* or its receptors. Bevacizumab, a monoclonal antibody that targets *VEGF*, is extensively utilized in the treatment of CRC. By neutralizing *VEGF*, bevacizumab effectively inhibits angiogenesis, depriving tumors of their blood supply and consequently suppressing growth and metastasis. It is crucial to consider predictive biomarkers in the context of anti-angiogenic therapies within precision medicine. Elevated *VEGF* levels in the tumor microenvironment correlate with poorer prognoses and more aggressive disease. Understanding the molecular mechanisms that drive *VEGF* overexpression is vital for developing personalized treatment strategies[123]. Anti-angiogenic therapies may be particularly effective for patients with specific genotypes or molecular characteristics that indicate a greater reliance on angiogenesis. The combination of anti-angiogenic therapies with other targeted agents, such as *EGFR* inhibitors, has been investigated to enhance efficacy, especially in patients with wild-type *RAS* genes. This approach aims to improve treatment outcomes and provide more tailored therapeutic options [124].

Targeted drugs for APC

Mutations in the *APC* gene are found in more than 80% of sporadic CRC cases. The *APC* protein comprises several functional domains that play roles in cell migration, adhesion, proliferation, differentiation, and chromosomal assembly. Changes in the APC gene represent an early event in the progression of CRC. The CMS2, CMS3, and CMS4 subtypes of CRC show a higher prevalence of *APC* mutations. Therapeutic agents aimed at *APC* in cancer treatment mainly concentrate on altering the *Wnt* signaling pathway (further details are available in section "8.2 targeted drugs for *Wnt* pathway"). Recent studies have provided new insights into targeting *APC*. Research by Shailesh indicated that statins

have a synthetic lethal effect on *APC*-mutated CRC cells by reducing *Wnt* signaling activity and lowering the expression of the anti-apoptotic protein survivin[125]. Wong *et al*[126] discovered that proprotein convertase subtilisin/kexin type 9 is significantly elevated in *APC*/*KRAS*-mutated CRC, promoting tumor cell proliferation *via KRAS/MEK/ERK* signaling. Proprotein convertase subtilisin/kexin type 9 inhibitors significantly inhibit the growth of *APC*/*KRAS*-mutated CRC cells and show synergistic effects when used alongside statins, suggesting that statins may serve as potential treatments for *APC*-mutated CRC. Cen *et al*'s study[127] demonstrated that *APC* mutations enhance the binding of the *β-catenin/TCF4* complex to the *PD-L1* promoter, increasing its transcription and allowing CRC cells to escape $CD8^+$ T-cell-mediated cytotoxicity. This highlights *APC*'s involvement in immune evasion and supports the development of novel therapies targeting *APC*-related immune escape mechanisms, such as inhibitors of *β-catenin* or *TCF4*. Investigational drugs targeting *APC* pathways have shown encouraging results in preclinical studies, including cyclooxygenase-2 inhibitors like celecoxib, which suppress tumor growth, and antibiotics like erythromycin, which restore *APC* function and decrease tumor numbers through nonsense mutation read-through[128]. Organoid technology, which mimics the complexities of the tumor microenvironment, supports research on *APC*-mutated CRC by enabling drug screening and efficacy assessment[129]. Gene therapy holds promise for restoring *APC* function by introducing the normal *APC* gene into cancer cells, thereby inhibiting tumor growth[130,131]. Although still in the experimental stage, encouraging results have been noted in CRC. Future research should focus on exploring *APC* mutations and CRC mechanisms, developing more effective targeted therapies, and integrating various treatment strategies to improve CRC therapeutic outcomes and enhance patient quality of life.

Targeted drugs for P53

The *P53* gene is pivotal in CRC development, with its mutations closely associated with tumor aggressiveness, resistance to chemotherapy, and unfavorable prognosis. Recent progress in *P53*-targeted drug development presents new treatment avenues. Small molecules like analog of PRIMA-1-246 bind to mutant *P53* proteins, restoring their wild-type conformation and tumor-suppressing capabilities. Similarly, maleimide-derived molecule-3 reactivates mutant *P53* by targeting its apoptotic pathways[132]. Another approach involves inhibiting the *P53*-mouse double minute 2 (*MDM2*) interaction, as *MDM2* negatively regulates *P53* by promoting its degradation. *MDM2* inhibitors such as nutlin-3a and AMG 232 disrupt this interaction and enhance *P53* activity, showing potential in tumor suppression[132]. *P53* mutations also lead to increased *PD-L1* expression, facilitating immune evasion, indicating a synergistic potential when combining *P53* reactivators with immune checkpoint inhibitors. Additionally, siRNA can silence mutant *P53* genes, while clustered regularly interspaced short palindromic repeats/clustered regularly interspaced short palindromic repeats-associated protein 9 editing offers the possibility of direct gene repair[133]. Despite promising clinical outcomes, challenges persist: The diversity of *P53* mutations necessitates personalized strategies, and issues such as drug toxicity, side effects, and resistance must be addressed to enhance safety and efficacy.

APPLICATION OF AI IN CRC

AI encompasses theories, methodologies, technologies, and applications that simulate and extend human intelligence through computational means[134]. Machine learning (ML) and DL are fundamental technologies within AI. ML allows computers to learn from data without explicit programming, while DL, a subset of ML, utilizes artificial neural networks to manage complex pattern recognition and prediction tasks through multi-layer abstraction and learning[135]. In medical imaging, DL emulates human cognitive processes to analyze data connections and learn features, emerging as a leading tool for tasks such as molecular prediction and CRC treatment. Prominent DL models include convolutional neural networks (CNN), recurrent neural networks, and Graph neural networks[136]. CNNs excel in image recognition, particularly in analyzing CRC pathology images to identify tumor morphology and immune infiltration. They automatically learn and transform features, simplifying model complexity through techniques like weight sharing. recurrent neural networks are adept at handling sequential data, making them useful for genomic analysis to predict patient responses to treatments. Graph neural networks process unstructured graph data, constructing molecular networks to forecast drug targets and therapeutic pathways[137]. Researchers train and assess DL models utilizing a variety of data types, including genomic, pathological imaging, and clinical information. Data preprocessing steps encompass normalization, feature extraction, and denoising to improve training efficiency and accuracy.

AI technology has extensive applications in the medical domain (Figure 6). In pathology, AI can autonomously identify tumor cells and features of the microenvironment in slides, aiding pathologists in diagnosis and classification. In imaging, AI assists healthcare professionals in analyzing computed tomography, magnetic resonance imaging, and 18F-fluoro-2-deoxyglucose positron emission tomography scans, thereby enhancing diagnostic precision and efficiency. In drug development, AI expedites screening and clinical trial design, leading to reduced costs and shorter timelines. In patient management, AI evaluates electronic medical records and physiological data to forecast disease progression and create personalized care plans[138]. AI presents distinct advantages in healthcare by efficiently processing vast amounts of genomic, radiomic, and clinical data, offering automated decision support to minimize human error. In CRC, AI holds considerable promise, as it can analyze multi-omics data (genomic, transcriptomic, proteomic, metabolomic) to discover new biomarkers and therapeutic targets. Furthermore, AI can formulate personalized treatment strategies based on patients' genomic and clinical profiles, thereby improving treatment outcomes[139].

Application of AI in molecular diagnosis in CRC

Molecular biomarkers are crucial for the diagnosis, treatment, and evaluation of CRC. AI technologies, including ML and

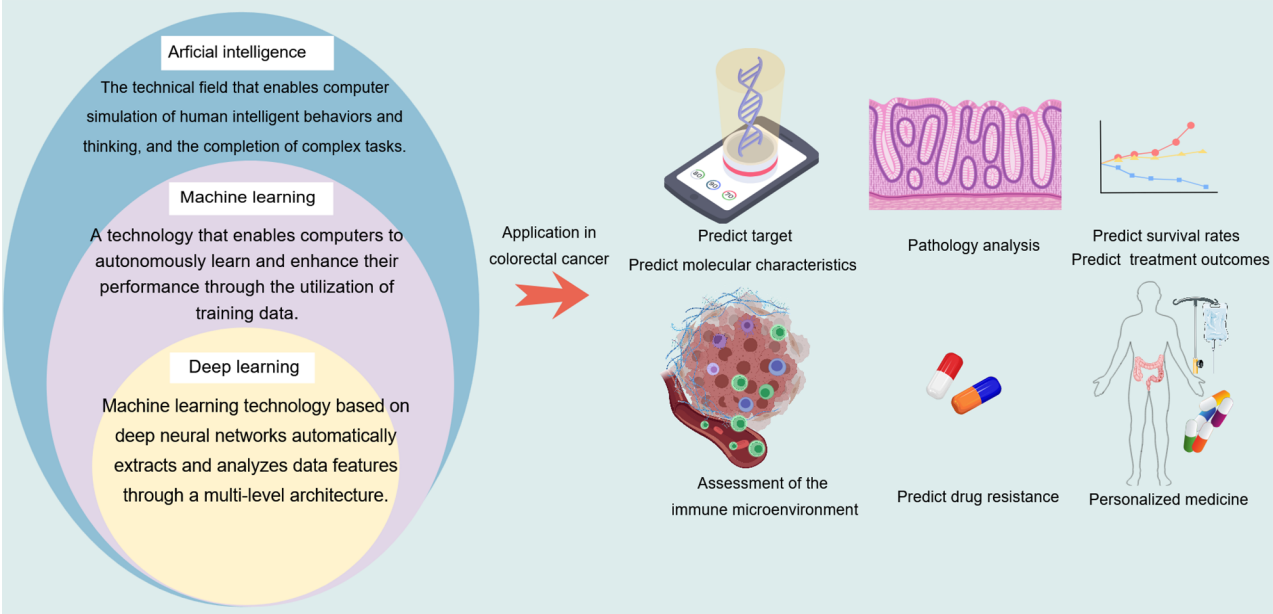

Figure 6 A comparison among artificial intelligence, machine learning, and deep learning, as well as their applications in the molecular diagnosis and treatment of colorectal cancer. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material.

DL, are increasingly utilized for the detection of molecular biomarkers to enhance efficiency, lower error rates, and improve clinical applicability. AI-driven image analysis and data modeling provide innovative approaches for identifying MSI/dMMR[140]. Specifically, CNNs can predict MSI/dMMR status directly from hematoxylin and eosin (HE)-stained pathological slides by learning from extensive image datasets. This automation minimizes manual intervention, reduces costs, and enhances accuracy compared to conventional methods[141]. Research by Hildebrand *et al*[142] demonstrated high accuracy in predicting MSI/dMMR using ML on high-quality datasets. However, accuracy significantly declines when applied to diverse racial or clinical cohorts. Current studies are focused on refining ML techniques for MSI prediction and comparing them with next-generation sequencing methods. Zamanitajeddin *et al*[143] introduced a novel approach that incorporates cellular network information into DL models. They constructed a cellular graph where cell nuclei serve as nodes and connections form edges, employing social network analysis to extract interpretable features. By integrating social network analysis features with DL in multiple instance learning frameworks, they enhanced predictions for CIN, *P53*, *BRAF*, and MSI status, achieving average area under the receiver operating characteristic increases of 2.4%-4% and area under the precision-recall curve increases of 7%-8.8%.

With advancements in molecular pathology and personalized treatment, CRC diagnosis and treatment have progressed to the molecular subtyping level. The four CRC CMSs (CMS1 to CMS4) provide a research framework, but traditional RNA sequencing for CMS classification is expensive and technically demanding. Recent developments in image analysis and DL facilitate CMS prediction from routine HE-stained slides. Sirinukunwattana *et al*'s team[144] created the Immunotherapy-based Cancer Management System, which, after multi-cohort training, improved model generalization and achieved finer spatial resolution for CMS classification. A NanoCMSer classifier based on NanoString technology also demonstrated high accuracy for fresh-frozen and formalin-fixed paraffin-embedded samples[144]. Bhukdee *et al*[145] utilized a 62-gene panel to identify new subgroups and elucidate CRC molecular mechanisms. These studies investigate AI applications in CRC molecular subtyping, providing technical support and theoretical foundations for precision medicine. Based on DL, this study developed a CRC molecular subtype classification system using high-quality whole-slide images annotated by pathologists. The system performed well on test sets, potentially reducing the workload of pathologists and advancing precise CRC treatments.

Pathological images and genomic data are vital in CRC research. Pathological images reveal tumor morphology, including cellular structure, tissue architecture, and immune infiltration, while genomic data uncover genetic variations and molecular mechanisms. The integration of these data types enhances the understanding of tumor biology, improving predictions of behavior and treatment responses[146]. AI algorithms, particularly DL, serve as effective tools for merging pathological images with genomic data. For instance, CNNs can process pathological images, extract features, and then jointly model these features with gene expression data to predict molecular subtypes or tumor prognosis[147]. This integration leverages both data types to improve prediction accuracy. The combination of digital pathology and AI will propel precision oncology forward, enabling personalized treatments. AI faces several limitations in the molecular diagnosis of CRC. Small sample sizes can lead to overfitting due to challenges in data collection, while inconsistent experimental methods and annotations, along with significant variations in data formats and distributions, hinder algorithm learning. These algorithms require a substantial number of labeled samples, and DL models often lack interpretability. Additionally, existing algorithms struggle to adapt to the dynamic changes in tumor mechanisms, with hyperparameter settings influencing their performance. Clinically, strict regulations, high costs, and lengthy timelines associated with large-scale multicenter trials present significant challenges. Traditional practices can obstruct the integration of new tools, necessitating retraining for healthcare providers, and ensuring data privacy remains a complex

issue.

Application of AI to evaluate tumor immune microenvironment in CRC

The tumor immune microenvironment's composition and its role in CRC progression are intricate. Its significance in predicting prognosis and evaluating immunotherapy is increasing, paving the way for new screening methods for populations sensitive to immunotherapy[148]. Traditional immunohistochemistry often fails to fully capture this complexity. AI algorithms can extract essential features from high-throughput data, such as single-cell sequencing and spatial transcriptomics, to characterize the immune microenvironment[149]. AI can analyze multiplex immunohistochemistry images, identify and quantify immune cells, and assess spatial relationships, leading to more accurate evaluations. Väyrynen *et al*[150] employed DL on HE-stained tissue microarray images to classify and count lymphocytes, plasma cells, neutrophils, and eosinophils in both epithelial and stromal regions of colorectal tumors, demonstrating its potential. Kather *et al*[151] utilized CNNs to identify stromal types in CRC, analyze gene expression profiles, pinpoint genes associated with immunotherapy responses, and create expression scores to predict responses to immune checkpoint inhibitors. AI-driven pathological image analysis will accelerate the assessment of complex tumor immune microenvironments, enhancing objectivity and reproducibility.

Application of AI to predictive models of drug targets and treatment response in CRC

AI algorithms, including ML and DL, are instrumental in identifying potential drug targets and validating their effectiveness through case studies. These models leverage molecular data, such as gene expression profiles and mutation states, to forecast patient responses to specific drugs[152]. Model performance is typically evaluated using metrics like area under the curve, sensitivity, and specificity, and validated through methods such as cross-validation and testing on external datasets. Predicting drug sensitivity remains a significant challenge in precision medicine. By analyzing genomic, transcriptomic, and drug response data from tumors, AI can predict drug responses to inform clinical decisions[153]. AI identifies biomarkers from gene expression, mutations, and copy number variations, uncovering key driver genes and pathways for drug development[154]. Despite AI's potential and efficiency in predicting drug targets for CRC, its application encounters challenges such as data dependency, biological complexity, clinical translation hurdles, and methodological flaws. Interdisciplinary collaboration, interpretable models, and improved experimental validation are essential for clinical progress.

AI algorithms also hold considerable promise in predicting responses to immunotherapy. By analyzing clinical, genomic, transcriptomic, and imaging data, they can forecast responses to immunotherapy and guide treatment decisions [155]. For instance, AI can evaluate tumor mutation burden, MSI, and *PD-L1* levels to predict responses to immune checkpoint inhibitors. Additionally, AI can dynamically monitor immune status to predict long-term efficacy. By analyzing blood samples for circulating tumor DNA, circulating tumor cells, and cytokines, AI can assess treatment responses and adjust therapies accordingly[156]. Schulz *et al*[157] developed a multi-stain DL model trained on over 1000 CRC patients, demonstrating superior prognostic accuracy and aiding in predicting treatment responses for rectal cancer [157]. Such tools facilitate patient stratification and resource allocation.

Application of AI in personalized treatment in CRC

Personalized treatment is crucial for CRC due to its inherent heterogeneity. AI models can integrate clinical history, molecular characteristics, and imaging data to formulate precise treatment plans. AI is utilized in chemotherapy, targeted therapy, and immunotherapy. It can predict chemotherapy efficacy and side effects based on genetic and tumor microenvironment information, optimizing treatment strategies[158]. For targeted therapy, AI assists in selecting appropriate drugs, thereby enhancing efficiency. In immunotherapy, AI predicts responses to immune checkpoint inhibitors, identifying patients most likely to benefit[159]. Sun *et al*[160] developed and validated a radiomics-based biomarker for tumor-infiltrating CD8 cells using ML, predicting responses to *PD-1/PD-L1* therapies based on computed tomography features. In CMS-based treatment for CRC, studies by Lafarge and Domingo highlighted AI's potential. Lafarge *et al*'s study[161] DL-based CMS identified significant correlations between CMS1 and pathological complete response post-long-course chemoradiotherapy by analyzing 1057 whole slide images. Lafarge *et al*[161] examined multi-omics data, confirming the association of CMS1 with radiosensitivity (odds ratio = 3.52, $P = 0.0119$) and created a predictive model for pathological complete response. These results underscore the importance of integrating AI with multi-omics data to accurately identify CMS subtypes and their treatment responses, thereby enhancing personalized care and improving patient outcomes. This progress paves the way for precision medicine based on CMS classification.

Solutions to data privacy and ethical issues of AI in healthcare

In medical AI applications, safeguarding patient data privacy is of utmost importance. Mishandling data can lead to significant legal and reputational repercussions, eroding patient trust. Currently, various strategies are employed to protect sensitive information. Differential privacy obscures individual data by introducing noise while maintaining statistical integrity. Homomorphic encryption allows computations on encrypted data without the need for decryption, thereby preserving privacy[162]. Secure multi-party computation facilitates collaborative computing without disclosing private information. In CRC research, these techniques safeguard genomic data, pathology images, and clinical information while enabling analysis and modeling. Ethical considerations in AI encompass informed consent, algorithmic bias, and accountability. Informed consent ensures that patients are fully aware of the purpose, risks, and benefits associated with the use of AI systems and voluntarily agree to data utilization. Algorithmic bias can lead to discriminatory outcomes, such as diminished diagnostic accuracy for non-white patients if the training data is skewed towards white patients[163]. Accountability issues arise regarding who is liable for AI errors - developers, users, or medical institutions.

These factors directly affect the rights of CRC patients; for instance, if an AI diagnostic system fails to detect a patient's cancer, it may result in delayed treatment.

To address privacy and ethical challenges, a comprehensive framework that encompasses technical, legal, and social dimensions is essential. Stringent regulations should delineate rules for data collection, usage, and sharing, with penalties for violations. Public education initiatives should raise awareness about data privacy and AI ethics, promoting informed consent. Transparency is equally crucial - designs and operations of AI systems should be disclosed for public scrutiny and evaluation[164]. For example, independent ethics committees could evaluate ethical risks associated with medical AI projects and offer guidance.

APPLICATION OF ORGANOIDS IN CRC

The intestinal epithelium, composed of a single layer of columnar cells that includes absorptive and secretory cells, plays a vital role in nutrient absorption and gut protection[165]. It is the fastest self-renewing tissue in adult mammals, with the villus-crypt structure renewing every 4-5 days (Figure 7). Intestinal stem cells located at the base of the crypt, supported by factors such as *Wnt*, R-spondin, epidermal growth factor, NOTCH, and Noggin from Paneth cells, proliferate and differentiate into mature intestinal cells. Sato *et al*[167] identified leucine-rich repeat-containing G-protein-coupled receptor 5 (a *Wnt* target gene) as a marker for intestinal stem cells[166]. Subsequently, Sato *et al*[167] discovered intestinal stem cells at the crypt base in normal mice and differentiated them into self-organizing "mini-gut" organoids with a crypt-villus structure, creating the first 3D organoid that retained crypt characteristics for up to 8 months. Spence *et al* [168] successfully generated human intestinal organoids from pluripotent stem cells by inducing definitive endoderm *via* activin A (a *TGF-β* molecule), treating them with a medium containing fibroblast growth factor 4 and Wnt3A to form hindgut spheroids, and transferring them to an organoid-promoting culture system, resulting in polarized columnar epithelial cells containing goblet, Paneth, and enteroendocrine cells.

Key components for culturing tumor organoids include initial cells, extracellular matrix, and growth regulators. Initial cells can be obtained by isolating cells directly from patient tumor tissues to create PDOs or by utilizing stem cells, such as embryonic, induced pluripotent, and adult stem cells, which self-organize into organoids with specific structures that mimic *in vivo* development (Figure 8). The extracellular matrix provides attachment points and directional growth support for the cells. Growth regulators, including pathway activators or inhibitors, are added to meet the organoid growth requirements at various stages[169]. For CRC organoids, essential factors include, the *Wnt* pathway activator R-spondin-1 protein, the bone morphogenetic proteins inhibitor Noggin protein, nicotinamide, and the tumor necrosis factor inhibitor A83-01[170]. Organoids, as 3D structures cultured in vitro, accurately replicate *in vivo* organ structures, functions, and physiological states, with extensive applications in CRC molecular mechanisms, drug screening, biobanking, and personalized medicine[171,172].

Application of organoids in molecular diagnosis in CRC

Single-cell RNA sequencing highlights the heterogeneity of PDOs, serving as a valuable tool for investigating tumor cell functions and their roles in tumor progression[173]. This technique identifies gene expression profiles across various cellular subpopulations and correlates them with clinical features, facilitating biomarker discovery related to tumor progression and therapeutic responses. In the context of CRC, it can detect diverse cell types, including tumor stem cells, immune cells, and stromal cells, while examining their interactions. This analysis helps elucidate how the tumor microenvironment affects growth and metastasis, thereby guiding targeted therapies. By comparing gene expression variations between drug-sensitive and drug-resistant tumor cells, researchers can uncover molecular mechanisms contributing to drug resistance, providing critical insights for developing strategies to overcome this challenge. For instance, certain subpopulations of tumor cells may display distinct gene expression patterns that make them less responsive to chemotherapy, directing clinicians toward alternative treatment options. The application of single-cell RNA sequencing technology allows for a comprehensive understanding of the intricate heterogeneity of tumors, thus providing essential information for devising more precise treatment strategies[174].

PDOs offer significant advantages in preserving genetic stability and modeling tumor heterogeneity. Compared to conventional 2D cell lines, organoids more effectively maintain the genetic characteristics of the original samples, ensuring the stability of genetic information during extended culture periods and enhancing the reliability of research findings. In cancer research, PDOs retain the genomic, transcriptomic, and epigenetic features of primary tumors, accurately simulating the cellular diversity within tumors[175]. Utilizing advanced techniques like single-cell sequencing, researchers can perform detailed analyses of gene expression profiles across different cell subpopulations within organoids, thereby providing robust support for investigations into tumor evolution, mechanisms of drug resistance, and personalized treatment strategies. Consequently, organoids have become essential tools in cancer research and translational medicine. However, organoids also face several limitations in the molecular diagnosis of CRC. Cultivation can be time-consuming and challenging, with success rates ranging from 30% to 60%, influenced by patient variability, tumor characteristics, and sample quality. Long-term culture poses risks of genetic drift and phenotypic alterations. In molecular detection, current techniques may be incompatible; impurities within organoids can interfere with results, and comprehensive molecular testing can be expensive. Clinically, the processes of organoid cultivation, testing, and result interpretation lack standardized protocols, regulatory approval processes remain unclear, and clinicians may require retraining to effectively utilize these new diagnostic tools.

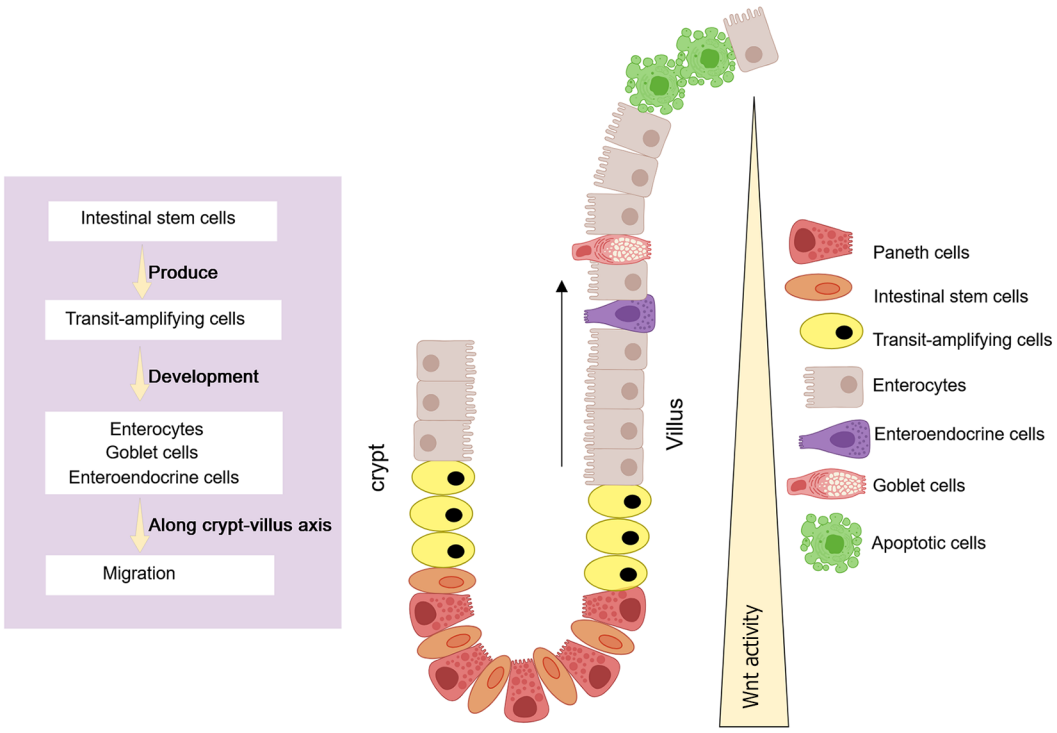

Figure 7 The intestinal crypt is composed of a specialized microenvironment. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. Intestinal stem cells drive crypt renewal and give rise to transamplifying cells, whereas Paneth cells secrete critical niche factors, such as Wnt, which is essential for maintaining the stem cell niche.

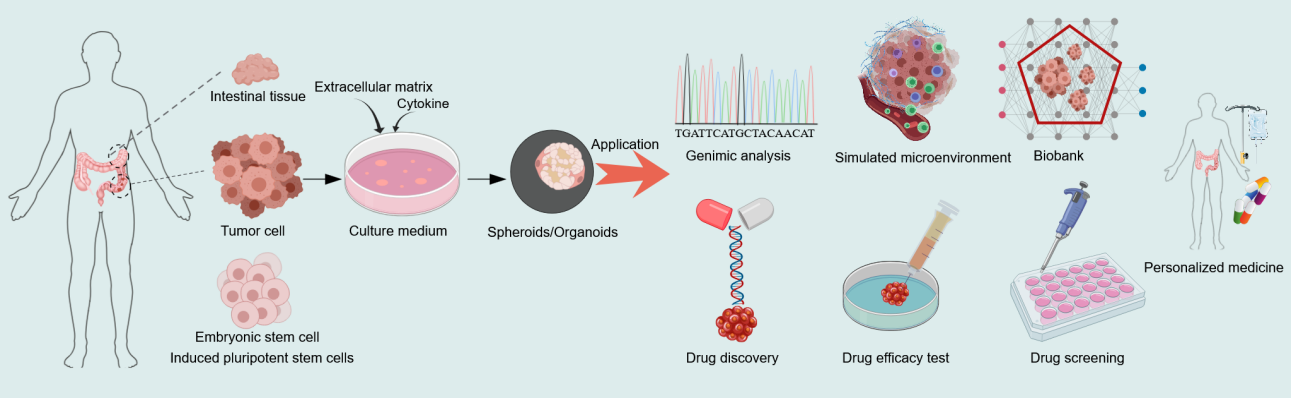

Figure 8 Schematic diagram of the establishment of artificial tissue cultures. Created with MedPeer (medpeer.cn). Copyright permission has been obtained in the Supplementary material. Tumor tissues from human intestines, stem cells from normal intestinal tissues and embryonic stem cells, as well as induced pluripotent stem cells, are embedded in the basement membrane matrix and maintained in the culture medium containing microenvironment factors crucial for proliferation.

Application of organoids in tumor immune microenvironment in CRC

A major advantage of organoids in tumor research is their ability to more accurately simulate the spatial organization and microenvironment of tumors more accurately than traditional 2D cell lines[176]. Organoids, with their three-dimensional structure, replicate the *in vivo* arrangement and interactions of tumor cells, capturing essential cell-cell and cell-matrix interactions that are critical for tumor growth, invasion, and metastasis. They can form various tissue structures, including tumor, stromal, and immune cells, reflecting the complexity of the tumor microenvironment. By manipulating culture conditions, researchers can introduce specific cell types or extracellular matrix components to replicate particular microenvironment features. For instance, incorporating vascular endothelial cells can enhance studies on tumor angiogenesis. Organoids also mimic dynamic tumor changes, such as invasion and metastasis[177]. For example, Qin *et al*[178] discovered that co-culturing mouse intestinal organoids with macrophages and fibroblasts can hyperactivate the *PI3K* signaling pathway in colon epithelial cells harboring *KRAS* and *P53* mutations. Dijkstra *et al*[179] demonstrated that co-culturing autologous tumor organoids with peripheral blood lymphocytes can enrich tumor-reactive T cells from the blood of MMR-deficient CRC patients. Researchers can investigate tumor behavior by observing changes in organoid

morphology, cell migration, and matrix degradation. These capabilities position organoids as a valuable platform for exploring tumor development and treatment, offering new avenues for creating more effective therapies.

Application of organoids in anticancer drug screening and new drug development in CRC

Drug resistance in CRC is a significant factor contributing to treatment failure. Tumor cells can develop resistance to chemotherapy and targeted therapies through mechanisms such as increased drug efflux, mutations in drug targets, pathway activation, and alterations in the tumor microenvironment[180]. PDOs can model the evolution of this resistance through long-term culture. For instance, resistance can be induced by gradually escalating drug concentrations, followed by genomic, transcriptomic, and proteomic analyses to elucidate the underlying resistance mechanisms[181]. Single-cell RNA sequencing can identify resistant subpopulations and highlight key genes and pathways associated with resistance. Research utilizing PDOs has revealed various molecular mechanisms responsible for CRC resistance[182]. The extracellular matrix and immune cells within the tumor microenvironment also play a role in influencing drug sensitivity. PDOs facilitate the examination of these factors, providing insights into overcoming resistance. PDOs, with their 3D structure, more effectively replicate the tumor microenvironment, preserving the heterogeneity and pharmacological characteristics of the original tumor. They excel in evaluating drug sensitivity and facilitate high-throughput screening. Automated platforms and image analysis enable rapid testing of numerous compounds, thereby expediting drug discovery[183]. In clinical settings, PDO-based drug sensitivity assays inform treatment decisions. For example, when resistance to first-line therapies arises, PDOs can assess alternative drugs or combinations to identify the most effective treatment options. Additionally, PDO-based screening aids in new drug development by identifying active compounds and potential therapeutic targets[184]. Despite the high biomimicry and individualized potential of organoid models in drug screening and new drug development for CRC, they encounter significant limitations: Inconsistent cultivation success rates (affected by tumor heterogeneity and sample quality), inadequate clinical relevance in drug sensitivity predictions (due to the absence of standardized evaluation systems), simplified microenvironments (lacking essential components like immune cells and vascular networks), and throughput limitations (making large-scale drug screening challenging). Future efforts should concentrate on optimizing cultivation systems, creating high-throughput platforms, and integrating multi-omics analyses to improve predictive accuracy and translational value.

Application of organoids in personalized treatment in CRC

PDOs play a crucial role in personalized treatment by accurately predicting patient responses through their ability to mimic tumor biology and heterogeneity. Research indicates that PDO drug sensitivity tests correlate strongly with clinical metrics such as ORRs and progression-free survival[185]. For instance, testing CRC PDOs with drugs corresponding to clinical treatments has shown high consistency with patient outcomes[186]. This suggests that PDOs can be employed to anticipate a patient's treatment response before clinical intervention, thereby assisting healthcare providers in selecting the most effective therapeutic strategies. Furthermore, PDOs can compare responses to various treatments, allowing for tailored plans for individual patients. Unlike genomics-based algorithms that rely solely on genetic mutations, PDOs reflect tumor cell function, microenvironment, and interactions, providing a more comprehensive approach to drug response prediction, making them a promising tool for future personalized therapies.

In addition to predicting treatment outcomes, PDOs exhibit significant potential in prognosis prediction and treatment optimization[187]. They can simulate characteristics such as tumor invasion, propensity for metastasis, and drug resistance, aiding physicians in identifying high-risk patients and formulating precise treatment plans. For example, studies have demonstrated that the invasive capabilities of certain PDOs correlate with the risk of tumor metastasis, while their resistance is associated with poor prognosis[188]. Additionally, PDOs can evaluate tumor responses to various therapies, enabling the selection of the most appropriate treatment plan by screening drug combinations or treatment options[189]. In terms of treatment optimization, PDOs can help overcome resistance or minimize side effects, such as identifying drug combinations to counteract resistance or assessing drug toxicity to select less harmful options. Additionally, PDOs facilitate the development of personalized immunotherapy by stimulating tumor PDOs for immune response analysis to identify suitable drugs[190]. However, most studies remain in preclinical phases, necessitating validation in larger clinical trials. Furthermore, PDO culture and analysis techniques require further standardization and refinement to ensure clinical reliability.

Establishment of organoids biobank in CRC

The creation of organoid biobanks is essential for advancing cancer research and facilitating clinical translation[191]. These biobanks provide vital resources for large-scale drug screening, fundamental research, and clinical applications. By establishing organoid libraries that encompass diverse tumor types, pathological features, and genetic backgrounds, researchers can access experimental materials more efficiently, thereby accelerating progress. Tumor organoid biobanks are increasingly important for investigating cancer mechanisms, exploring treatment options, and developing new drugs [192]. Yao *et al*[193] established an organoid biobank from patients enrolled in phase III clinical trials for locally advanced rectal cancer who received neoadjuvant chemoradiotherapy. Their research confirmed that these rectal cancer organoids accurately reflect the pathophysiology and genetic alterations of the corresponding tumors, demonstrating a high degree of concordance between patient responses to chemoradiotherapy and organoid responses. Yan *et al*[194] addressed a gap in existing CRC models by creating an organoid biobank enriched for sporadic early-onset CRC, revealing distinct genetic profiles and novel pathway synergies. The study by Yao *et al*[195] further illustrated the potential of tumor organoids to predict clinical responses to chemotherapy in advanced CRC.

However, the construction of biobanks presents numerous technical challenges. First, the long-term preservation of organoids is problematic, as current cryopreservation methods may compromise their viability and properties,

necessitating the development of more effective techniques. Second, the culture conditions for organoids are complex, requiring stringent quality control systems to ensure consistency[196]. Additionally, a standardized data management system is essential for managing diverse information, and unified data-sharing platforms must resolve inconsistencies across different laboratories. Researchers should investigate advanced cryopreservation methods, automated cultivation systems, and standardized data management solutions to improve the efficiency and reliability of biobanks.

The creation and utilization of organoid biobanks necessitate the protection of patient privacy and strict adherence to ethical guidelines. Since organoids are derived from patient tissue samples that contain genetic and pathological information, it is crucial to implement measures that safeguard patient privacy. First, informed consent must be secured by clearly explaining the purpose, content, and risks associated with organoid research, ensuring that patients have the right to decline participation. Second, patient information should be anonymized, separating personal details from research data to prevent any potential leaks of sensitive information. Furthermore, stringent access control measures must be established, allowing only authorized personnel to access relevant data. Ethical guidelines should strike a balance between scientific research and patient rights, respecting autonomy, informed consent, and privacy. This can be accomplished by drawing from practices in other fields, such as forming ethics review committees to evaluate and oversee research protocols, and implementing regulations to govern organoid biobank management, ensuring transparency and compliance in research. These measures can facilitate scientific advancement while safeguarding patient rights to the fullest extent.

CONCLUSION

CRC, a prevalent and highly lethal malignancy worldwide, has experienced significant advancements in genetics and treatment in recent years. Sequencing technologies have enhanced our understanding of the genetic mechanisms underlying CRC, identifying numerous genetic variants associated with disease risk and molecular subtypes. These subtypes lay the groundwork for precision medicine, enabling tailored predictions of disease progression and treatment responses. On the therapeutic front, targeted therapies, such as anti-*EGFR* and anti-*TGF-β* agents, have improved survival rates and quality of life for patients. Immunotherapy has demonstrated remarkable efficacy in MSI-H/dMMR CRC, providing new hope for patients. Furthermore, multidisciplinary approaches that integrate surgery, chemotherapy, radiotherapy, and emerging methods are achieving personalized and precise treatment outcomes.

In this context, AI and organoid open new paths for CRC research. AI uses ML and DL to analyze complex biological data, such as gene expression profiles and imaging data, thereby accelerating the development of diagnostic models and personalized treatment strategies. AI enhances accuracy and efficiency in early diagnosis, particularly in the analysis of pathology slides, and predicts drug responses to assist in treatment selection. Meanwhile, organoid technology provides a more realistic *in vitro* model that simulates the *in vivo* environment for personalized drug screening and mechanistic studies. Compared to traditional cell lines, organoids more effectively replicate the tumor microenvironment, advancing our understanding of tumor behavior and therapy development.

However, this field faces numerous challenges. Despite significant progress in genetic research, the functions and interaction mechanisms of many genetic variations remain unclear, limiting the translation of genetic information into effective treatments. While targeted therapies and immunotherapies have shown impressive results, both primary and acquired resistance significantly affect long-term efficacy. Additionally, optimizing multidisciplinary treatment plans to ensure seamless integration and synergy among various approaches remains a critical challenge. In AI applications, issues related to data quality, standardization, and privacy protection are pressing concerns. Variability and inconsistencies in genetic and clinical data can hinder the performance of AI models and their widespread adoption. Ensuring patient data privacy is also a fundamental prerequisite for the integration of AI in healthcare. In organoid technology, although organoids can mimic tumor microenvironments, they still fall short of fully replicating human complexity, and challenges such as standardization, long-term stability, and precise environmental matching require further investigation.

Future CRC research and treatment should prioritize understanding genetic mechanisms to develop targeted therapies, explore strategies to overcome resistance, such as combination treatments or drug innovations, and continuously refine multidisciplinary approaches to enhance overall outcomes. The integration of AI, organoid technology, and genetic research holds promise for addressing current challenges. Establishing large-scale, high-quality genetic and organoid databases, combined with AI's analytical capabilities, will advance precision medicine in CRC. At the same time, improving the translation of basic research into clinical applications and expediting the transition of novel technologies from the laboratory to clinical settings will provide more effective treatment options for CRC patients, significantly enhancing their survival rates and quality of life.

FOOTNOTES

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