



REVIEW

Multi-omics in colorectal cancer liver metastasis: applications and research advances

Kexue Zhou¹, Chengxiang Yang¹, Yan Li^{1,2}

¹School of Medicine Chongqing University, Chongqing 400030, China; ²Department of Medical Oncology, Chongqing University Cancer Hospital, Chongqing 400030, China

ABSTRACT

Colorectal cancer (CRC) is a common malignant tumor with a high mortality rate worldwide. Advanced CRC often leads to liver metastasis, which has a poor prognosis, highlighting the need to investigate the underlying mechanisms. Omics, encompassing genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics, enables comprehensive molecular analysis of cells and tissues. Tumor-omics research has advanced rapidly, with growing attention on CRC-related omics. However, systematic reviews on omics research specific to colorectal cancer liver metastasis (CRLM) are limited. This review summarizes the current status and progress of multi-omics research on CRLM and discusses the application of multi-omics technologies in basic research and the significant clinical implications.

KEYWORDS

Colorectal cancer liver metastasis; genomics; transcriptomics; epigenomics; proteomics; metabolomics; microbiomics

Introduction

Global Cancer Observatory (GLOBOCAN) data from 2022 report 1.9 million colorectal cancer (CRC) cases and 904,000 deaths globally, ranking 3rd in incidence and 2nd in mortality worldwide¹. Between 25% and 30% of patients with CRC develop liver metastases with a poor prognosis and a 5-year survival rate < 10%^{2,3}. Studies on isolated cellular pathways and tissue metabolism offer limited insight into the pathogenesis of colorectal cancer liver metastasis (CRLM), diagnostic accuracy, recurrence, metastasis, therapeutic efficacy, and patient survival. Therefore, omics research significantly contributes to advancing our understanding of liver metastasis in patients with CRC.

Omics analysis involves statistical processing, and comparative and correlation analyses of bulk data across various molecular levels, such as genomics, epigenomics, transcriptomics,

proteomics, metabolomics, and microbiomics. Omics analysis establishes relationships among molecular data and reveals the interconnections⁴. For example, multi-omics research on CRLM integrates omics data to identify key genes, metabolites, proteins, and microorganisms involved in the process for further experimental analysis and potential applications.

Although there are numerous reports on omics research in CRC, systematic reviews on omics in liver metastasis are lacking. This study provides a comprehensive review of genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and multi-omics CRLM studies and explores the current state of omics research in this context (**Figure 1**).

Genomic insights into CRLM

Genomics explores the structure, dynamics, and functions of the genome. Ki et al.⁵ utilized complementary (c)DNA microarrays to identify 46 genes potentially involved in CRLM progression. Similarly, Yamasaki et al.⁶ showed that the potential for liver metastasis in CRC is encoded within the primary tumor and detected by gene expression profiling. Studies in China identified frequent mutations in patients with CRC with liver metastasis, including tumor protein (TP) 53 (82%), adenomatous polyposis coli (APC) (76%), Kirsten rat sarcoma viral oncogene homolog (KRAS) (42%), SMAD family member (SMAD) 4 (14%), filaggrin (FLG) (13%), and f-box and

Correspondence to: Yan Li

E-mail: pipili@sina.com

ORCID ID: <https://orcid.org/0000-0002-1830-2766>

Received February 11, 2025; accepted May 14, 2025;

published online June 26, 2025.

Available at www.cancerbiomed.org

©2025 The Authors. Creative Commons Attribution-NonCommercial

4.0 International License

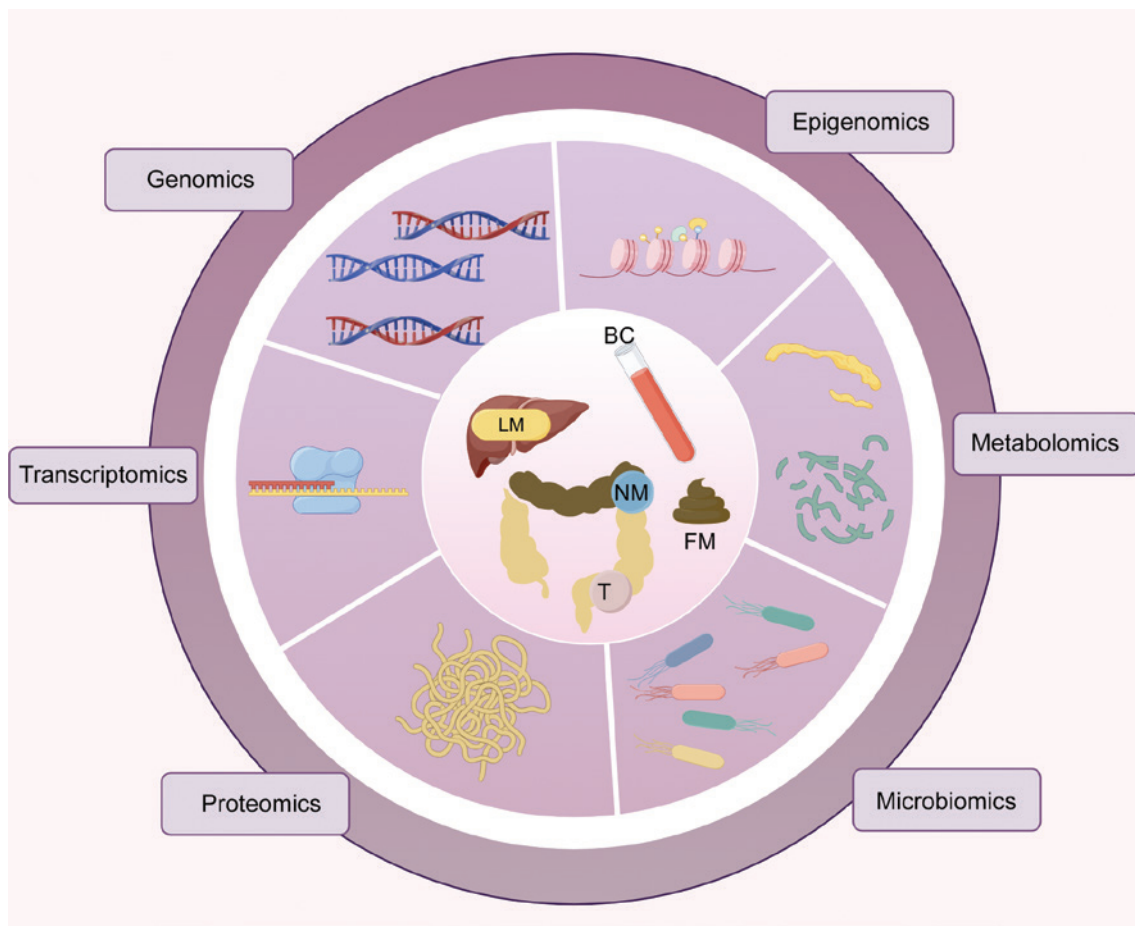


Figure 1 Omics framework of colorectal cancer liver metastasis. Genomic, epigenetic, transcriptomic, proteomic, metabolomic, and microbiomic analyses were performed on tissue from primary colorectal cancer lesions (T), liver metastases (LM), lymph node metastases (NM), blood circulation (BC), and fecal microbiota (FM) samples.

wd repeat domain-containing (FBXW) 7 (11%)⁷. These findings link high-frequency mutations to poor patient prognosis, thereby highlighting the clinical implications of genomic research for CRLM treatment and prognosis.

Genomic differences between primary CRC lesions and liver metastasis

Although significant research has focused on the genomics of primary CRC tumors, studies involving liver metastasis are limited. Evidence suggests that differential gene expression between primary and metastatic sites is a key genomic feature of liver metastasis. Lin et al.⁸ performed gene ontology (GO) analysis and showed that genes associated with tissue remodeling and immune responses are upregulated in metastatic tumors, whereas genes related to proliferation and oxidative

phosphorylation are downregulated. The study also identified 10 genes with higher expression in CRLM, 5 of which encoded “matrix proteins” involved in extracellular matrix (ECM) interactions, indicating a potential association with liver metastasis⁹. Notably, genomic profiles in patients with CRC vary significantly by metastasis site, with greater genomic divergence between primary tumors and liver metastases than between primary tumors and lung metastases¹⁰. Comparative genomic hybridization (CGH) and other techniques demonstrated a greater number of mutations in liver metastases than in primary tumors, which likely reflects increased genetic instability¹¹. Additionally, patients with sporadic CRLM exhibited specific transcriptional dysregulation in liver metastases, whereas primary tumor expression remained normal. This finding indicates increased genomic instability in metastatic cells or adaptive changes to the liver microenvironment^{12,13}.

Application of genomics in the tumor microenvironment (TME) of CRLM

Traditional sequencing methods treat tumor samples as a whole, whereas single-cell technologies differentiate cellular components, particularly immune cells. This shift has redirected cancer genomics from focusing solely on cancer cells to exploring the TME. Genomic analyses have revealed that immune cell changes within the TME may contribute to tumor progression and liver metastasis. Jackstadt et al.¹⁴ found that intestinal epithelial neurogenic locus notch homolog protein (NOTCH) 1 signaling drives metastasis through transforming growth factor (TGF)-dependent neutrophil recruitment, highlighting the role of NOTCH1 in CRC progression. Sathe et al.¹⁵ identified distinct intercellular communication programs in which macrophages and fibroblasts regulate the pre-metastatic niche in the liver, thereby forming a “soil” for tumor seeding. Specifically, TME-associated macrophages expressing secreted phosphoprotein (SPP) 1 promote primary CRC progression. Furthermore, Rong et al.¹⁶ used single-cell RNA sequencing to identify matrix gla protein (MGP) as a driver of CD8+ T cell exhaustion *via* NF- κ B activation for CRLM. MGP knock-out combined with anti-PD1 therapy synergistically resist liver metastasis. These findings highlight the role of genomics in understanding CRLM mechanisms and treatment outcomes.

Application of genomics in imaging diagnosis of CRLM

Studies linking genomics and imaging have proven valuable in diagnosing CRLM. Using next-generation sequencing (NGS) technology, a study analyzed weak target tumor enhancement (TTE) and normal tissues using CRC magnetic resonance imaging (MRI) and revealed correlations between TTE and genetic mutations in CRLM¹⁷. Wang et al.¹⁸ identified six genes (*NRAS*, *KRAS*, *BRAF*, *PIK3CA*, *MAPK1*, and *STAT1*) linked to specific imaging features, such as shape-elongation and gradient, thus providing a foundation for non-invasive diagnosis of liver metastasis.

Application of genomics in the treatment of CRLM

Surgery remains a viable option for patients with CRLM who meet resectability criteria. However, tumor molecular behavior, rather than surgical technique, ultimately determines

patient prognosis¹⁹. Chan et al.²⁰ reported no statistically significant differences in patient outcomes across surgical approaches. Chan et al.²⁰ emphasized the importance of integrated management strategies based on cancer genomics to assess prognosis. Genomic analysis can guide patient selection, surgical timing, and technique for metastatic lesions²¹. Sun et al.²² demonstrated that P-cadherin regulates CRLM. This finding suggested P-cadherin inhibition as a potential therapeutic strategy. Liu et al.²³ identified ankyrin repeat domain 42 (*ANKRD42*) as a key regulatory gene promoting CRLM through genome-wide sgRNA library screening. Knockdown of *ANKRD42* significantly attenuates tumor cell migration and invasion, highlighting its potential as a therapeutic target. Additionally, combining oxaliplatin with mTOR inhibitors shows synergistic effects, highlighting the potential of integrating chemotherapy with targeted therapy²⁴. While genomic analysis offers significant insights for CRC treatment, further research is warranted to advance clinical application.

Application of genomics in prognosis of CRLM

Genomic research can reveal the clonality and timing of metastatic CRC²⁵. Recent studies have focused on identifying biomarkers in bodily fluids, such as blood and urine, including serum proteins (peptides), plasma miRNAs, circulating tumor cells, and nucleic acids. When combined with technologies, such as whole-genome sequencing and circulating tumor cell DNA analysis, genomic analysis can help predict CRLM occurrence. Notably, undetectable circulating tumor DNA following liver metastasis resection suggests a better prognosis for recurrence-free survival²⁶.

The core of tumor genomics is mapping cancer-driving factors and providing personalized therapeutic strategies²⁷. Genomics is crucial in understanding CRLM origins, molecular differences between primary and metastatic lesions, genetic profiling, treatment decisions, and survival prognosis.

Epigenomics of CRLM

Although every human body cell contains the same genome, distinct cellular phenotypes arise from different gene expression patterns, driven by cell type-specific transcription factors and epigenome structures²⁸. Epigenomics primarily focuses on DNA and histone modifications that regulate chromatin structure, gene activity, and gene expression without altering the

DNA sequence⁴. Studies have suggested that epigenetic regulation may contribute to tumor metastasis²⁹, and DNA methylation and histone modifications are reversible. Investigating epigenetics in CRLM could reveal new therapeutic targets for CRLM diagnosis and treatment (**Figure 2**).

Relationship between DNA methylation and the occurrence, development, treatment, and prognosis of CRLM

DNA methylation occurs at cytosine residues preceding guanine in humans, forming CpG dinucleotides (C-phosphate-G bonds)³⁰. While most CpG dinucleotides are methylated, CpG islands, found in the promoter regions of 40%–60% of tumor suppressor genes, remain unmethylated in healthy cells. These islands, spanning 200–2,000 base pairs with a CG content $\geq$ 50%, contribute to gene expression regulation^{30–32}. Epigenetic mutations silence tumor suppressor genes or activate oncogenes in human cancers.

The methylation of various tumor suppressor genes is associated with CRLM. Zhang et al.³³ noted that long non-coding RNA (lnc-LALC) promotes CRLM by epigenetically silencing leucine zipper tumor suppressor gene 1 (*LZTS1*). Upregulation of genes, such as *SLC10A1*, *MAPT*, *SHANK2*, *PTH1R*, and *C2*, and downregulation of genes, including *CAB39*, *CFLAR*, *CTSC*, *THBS1*, and *TRAPPC3*, are linked to DNA methylation and may act as biomarkers for CRLM³⁴. Differential DNA methylation in primary CRC can predict risk of liver metastasis, with several regions, including *TNNI2*, *PAX8*, *GUF1*, *KLF4*, *EVI2B*, *CEP112*, and lncRNA *AC011298*, identified as prognostic biomarkers^{35,36}.

Numerous studies have observed hypermethylation of genes in metastatic liver lesions of CRC. Ebert et al.³⁷ found frequent hypermethylation of *TPEF*, which encodes a transmembrane protein with epidermal growth factor and follistatin domains, in primary CRC lesions and liver metastases. This finding suggested that epigenetic alterations are common in the early and late stages of carcinogenesis. Therefore, *TPEF* methylation may act as a diagnostic target. Several studies have identified different gene methylation mechanisms associated with CRLM. *ALX4* is hypermethylated in primary colorectal adenocarcinomas and liver metastases³⁸, and *MUC2* promoter methylation is linked to liver and lymph node metastases³⁹. Lu et al.⁴⁰ showed that *B3GNT7* methylation enhances CRC cell metastasis to the liver. Tommasi et al.⁴¹ found that *RASSF1A* methylation contributes to liver metastasis progression. Ju et al.⁴² suggested that DNA

methylation-induced silencing of *UPK3A* enhances liver metastasis CRLM. Rodger et al.⁴³ observed differential CpG methylation patterns, with hypomethylation in normal colon and primary CRC, but hypermethylation in liver metastases, which correlated with methylation levels and chromatin activity⁴⁴.

DNA methylation is a valuable tool for the prognostic assessment of CRLM. For example, multiplex DNA methylation profiling of circulating free DNA (cfDNA) enables patient stratification and treatment monitoring in advanced CRC with liver metastasis⁴⁵. Furthermore, methylation profiling has been used to identify effective methylation biomarkers, such as the significant increase in trichohyaline (*TCHH*) gene methylation, which correlates strongly with liver metastasis tumor volume. This finding suggested the potential of *TCHH* as a biomarker for liver metastasis⁴⁶.

Epigenetic regulation is reversible and restoring normal epigenomic profiles could serve as a potential therapeutic target for cancer. *CXCL14*, a tumor suppressor gene in CRC, is activated but silenced during progression, primarily because of promoter hypermethylation. Therefore, reversing *CXCL14* hypermethylation may offer an epigenetic therapeutic strategy for CRC treatment⁴⁷. However, research on epigenetic therapies to intervene in CRLM is limited and further exploration is needed.

Relationship between histone modifications and the occurrence, development, treatment, and prognosis of CRLM

DNA wraps around nucleosome particles to form the organizational foundation for eukaryotic genomes. Core histones (H2A, H2B, H3, and H4) undergo post-translational modifications that help define specific chromatin regions and states⁴⁸. These modifications include methylation, acetylation, ubiquitination, and phosphorylation with methylation and acetylation being most common⁴⁹. CRLM has been reported to be closely linked to histone modifications⁵⁰.

Histone methylation and demethylation in CRLM

Histone methylation involves adding methyl groups to lysine (K) residues on H3 and H4, and is a key post-translational modification⁵¹. Regulation of histone methylation is controlled by two enzyme groups [histone methyltransferases (HMTs), which add methylation marks, and histone demethylases (HDMs), which remove methylation marks]^{52,53}. Each lysine residue can undergo three distinct methylation states (monomethyl, dimethyl, or trimethyl)⁵⁴.

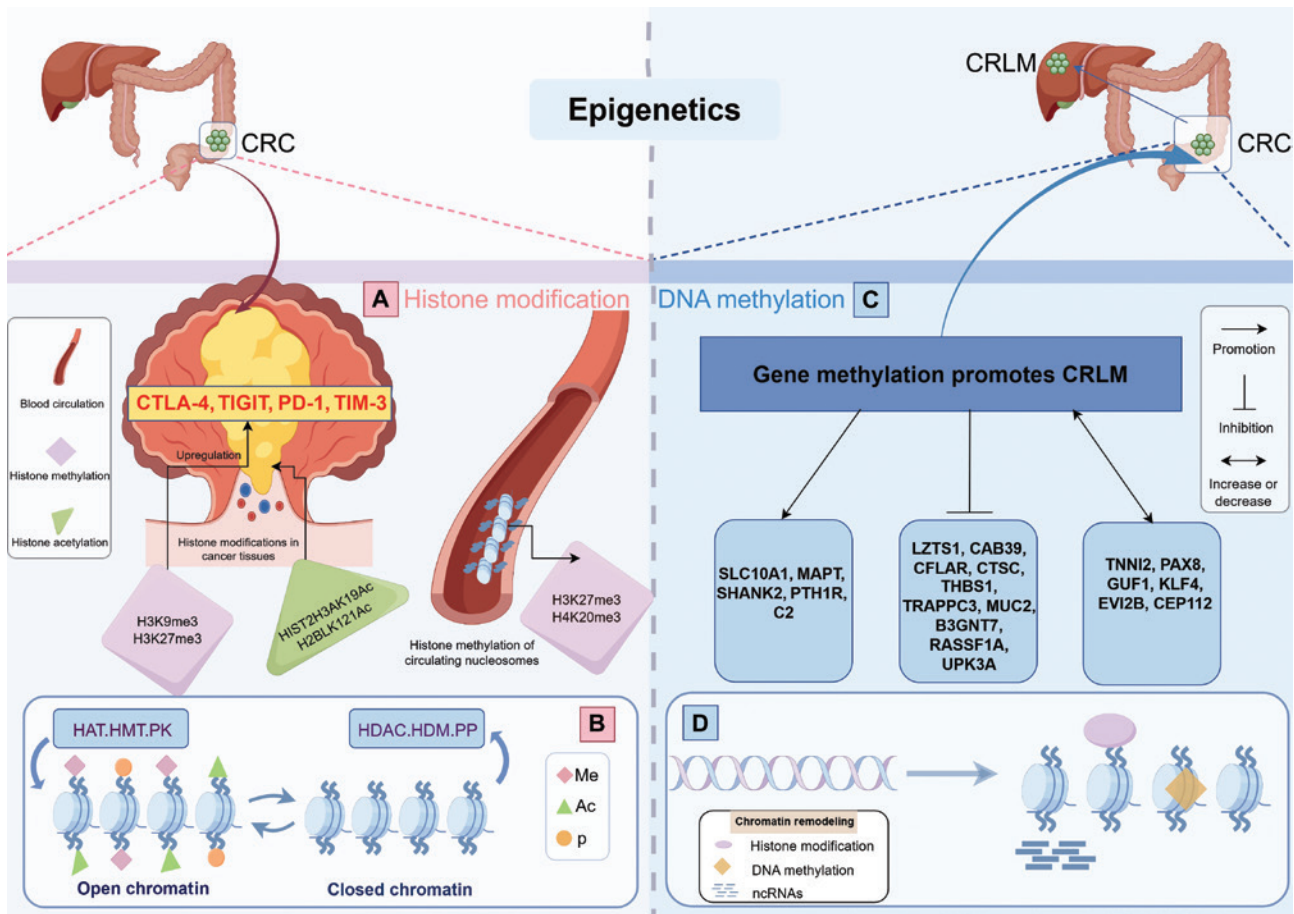


Figure 2 Epigenetic regulation in colorectal cancer (CRC) and CRC liver metastasis (CRLM). (A) Histone modifications as potential diagnostic biomarkers for CRC. Trimethylation of H3K9 and H3K27 enhances the expression of immune checkpoint genes, such as *CTLA-4*, *TIGIT*, *PD-1*, and *TIM-3*, which may serve as epigenetic markers for CRC. Methylation signatures on circulating nucleosomal histones, including H3K27me3 and H4K20me3, are detectable in the bloodstream and have potential diagnostic value. Differences in HIST2H3AK19Ac and H2BLK121Ac acetylation between primary CRC tumors and liver metastases may serve as biomarkers of CRC progression. (B) Schematic representation of histone modifications. Histone methylation, acetylation, and phosphorylation are dynamically regulated by histone methyltransferases (HMTs), histone demethylases (HDMs), histone acetyltransferases (HATs), histone deacetylases (HDACs), protein kinases (PKs), and protein phosphatases (PPs), resulting in chromatin remodeling toward either an open (active) or closed (repressive) state. (C) Role of DNA methylation in CRLM. Aberrant DNA methylation alters gene expression by promoting either transcriptional activation or repression, contributing to the progression of liver metastasis in CRC. (D) Schematic of epigenetic regulation via chromatin remodeling. Epigenetic mechanisms, including histone modifications, DNA methylation, and non-coding RNAs (ncRNAs), mediate chromatin structure reorganization, thereby influencing gene accessibility and transcriptional activity. B3GNT7, beta-1,3-N-acetylglucosaminyltransferase 7; CAB39, calcium-binding protein 39; C2, complement component 2; CEP112, centrosomal protein 112; CFLAR, CASP8 and FADD-like apoptosis regulator; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTSC, cathepsin C; EVI2B, ecotropic viral integration site 2B; GUF1, GUF1 homolog, GTPase; KLF4, Kruppel-like factor 4; LZTS1, leucine zipper tumor suppressor 1; MAPT, microtubule-associated protein tau; MUC2, mucin 2; PAX8, paired box 8; PD-1, programmed cell death protein 1; PTH1R, parathyroid hormone 1 receptor; RASSF1A, ras association domain family member 1 isoform A; SHANK2, SH3 and multiple ankyrin repeat domains 2; SLC10A1, solute carrier family 10 member 1; THBS1, thrombospondin 1; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM3, T-cell immunoglobulin and mucin-domain containing-3; TNNI2, troponin I2, fast skeletal type; TRAPPC3, trafficking protein particle complex subunit 3; UPK3A, uroplakin 3A.

Histone methylation modifications are reportedly involved in CRC initiation and progression⁵⁵⁻⁵⁷. However, research on the role of histone methylation modifications in liver

metastasis is limited. Tamagawa et al.⁵⁰ found that liver metastasis in CRC is associated with histone modifications with H3K27me2 and H3K4me2 methylation levels potentially

serving as independent prognostic factors⁵⁸. Specifically, lower H3K4me2 levels correlate with poorer survival outcomes⁵⁰. Further research is required to determine the role of histone methylation in CRLM.

Additionally, histone methylation modifications can serve as diagnostic markers for CRC⁵⁹ and predictors of chemotherapy sensitivity⁶⁰. Nair et al.⁶¹ compared the epigenetic modification mechanisms of immune checkpoints in CRC tissues and normal intestinal mucosa. Nair et al.⁶¹ found high expression of PD-1, CTLA-4, TIM-3, TIGIT, PD-L1, and Galectin-9 in CRC tissues. Nair et al.⁶¹ also observed a significant reduction in H3K9me3 binding to the PD-1 and TIGIT promoters and H3K27me3 binding to the CTLA-4 promoter in CRC tissues, as well as lower binding of both repressive histones to the TIM-3 promoter. These findings suggested that H3K9me3 and H3K27me3 are involved in upregulating CTLA-4, TIGIT, and PD-1, making these modifications potential diagnostic biomarkers for CRC.

Along with the gene methylation detected in tissues, histone methylation of circulating nucleosomes (H3K27me3 and H4K20me3) can serve as a biomarker for CRC diagnosis⁵⁹. Kang et al.⁶⁰ found that 5-fluorouracil (5-FU)-resistant colon cancer cells exhibit oxidative stress, which induces histone methylation-related proteins and DNA demethylases, thereby contributing to 5-FU resistance. However, the role of histone methylation modifications in predicting liver metastasis and survival prognosis remains unexplored.

Histone acetylation and deacetylation in CRLM

Histone acetylation is regulated by a balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs)⁶². Shen et al.⁶³ compared acetylation patterns in metastatic liver tumors and primary CRC tissues, and identified 31 downregulated acetylation sites on 22 proteins and 40 upregulated acetylation sites on 32 proteins. The most significantly altered acetylated histones were HIST2H3AK19Ac and H2BLK121Ac, which provides new insights into CRC metastasis. HDAC6-dependent deacetylation of A-kinase-anchoring protein 12 (AKAP12) leads to its ubiquitin-mediated degradation and promotes colon cancer metastasis⁶⁴. These studies suggest that histone acetylation and deacetylation are involved in CRC metastasis. However, liver metastasis-specific research has been limited.

CRLM transcriptomics

Although each distinct cell type shares an identical genome in multicellular organisms, not all genes are transcriptionally

active. Different cell types exhibit unique gene expression profiles. Transcriptomics classifies all types of transcripts, including mRNAs, ncRNAs, and miRNAs. The transcriptional structure of genes is determined by factors, such as the transcriptional start sites, 5' and 3' ends, splicing patterns, and other post-transcriptional modifications. Additionally, transcriptomics quantifies changes in the level of each transcript expression during development and under various conditions⁶⁵.

Transcriptomic study on the occurrence and development of CRLM

Researchers have elucidated the mechanisms driving CRLM based on transcriptomic analysis, which has provided insights into potential diagnostic biomarkers and therapeutic targets. Sha et al.⁶⁶ demonstrated that single-cell transcriptomic analysis can identify the potential cellular origin and driving factors of CRLM. Additionally, whole exome and RNA sequencing of CRC tumors and liver metastases revealed that copy number variations primarily follow several evolutionary patterns, such as clonal-clonal evolution 20q amplification (amp), 17p deletion (del), 18q del, 8p del, subclonal-clonal evolution (8q amp, 13q amp, and 8p del), and metastasis-specific evolution (8q amp).

These findings suggested a novel evolutionary process for CRLM⁶⁷ and offer deeper insights into the mechanisms underlying liver metastasis through transcriptomics. The liver-specific transcription factors, FOXA2 and HNF1A, can reportedly bind to acquired enhancers and activate the transcription of liver-specific genes, thereby driving CRLM⁶⁸. Cai et al.⁶⁹ reported that polyclonal dissemination and transcriptional repressor GATA binding 1 (*TRPS1*) gene mutations may be key drivers of CRLM through single-cell exome sequencing. Hur et al.⁷⁰ concluded that upregulated miR-885 and miR-122 and downregulated miR-10b in CRLM tissues suggests the potential as metastasis-specific biomarkers⁷¹. Furthermore, high expression of miR-20a is closely associated with the liver metastatic state of CRC⁷². Xu et al.⁷³ found that circRNA_0001178 and circRNA_0000826 are significantly upregulated in CRLM tissues, suggesting that these circRNAs may serve as potential biomarkers for predicting CRLM.

Hematogenous dissemination is the primary route for CRLM, followed by two histopathologic growth patterns [sprouting angiogenesis and vessel co-option (VCO)]. Transcriptomic research has revealed distinct mechanisms

for both metastatic patterns. Most liver metastases promote hematogenous spread through angiogenesis. Fleischer et al.⁷⁴ found specific metabolic changes and WNT signaling activation in VCO-related metastatic cancer cells, providing potential therapeutic targets for VCO-based CRLM. Tumor pericytes (TPCs) play a pivotal role in this invasion. Li et al.⁷⁵ used single-cell RNA sequencing (scRNA-seq) to identify 13 TPC subpopulations and a novel TCF21^{high} “matrix-pericytes” phenotype, which promotes extracellular matrix stiffness, collagen remodeling, and metastasis. Rad et al.⁷⁶ found that runt-related transcription factor-1 (RUNX1) overexpression in replacement lesions drives cancer cell motility in VCO-type CRLM.

Transcriptional differences between primary CRC lesions and liver metastases

Various researchers have compared the transcriptomic profiles of primary CRC lesions and liver metastases to determine transcriptional heterogeneity and cellular diversity. Liver metastases exhibit lower expression of miR-99b-5p, miR-377, miR-143, miR-10b, miR-28-5p, and miR-200c compared to primary tumor tissues, while miR-196b-5p, miR-122, miR-122*, and miR-885-5p are upregulated^{71,77}. Four lncRNAs (GAS5, H19, MEG3, and Yiyi) also exhibit significant differences⁷⁸. Wang et al.⁷⁹ identified increased CD8_CXCL13 and CD4_CXCL13 subpopulations in liver metastases, which are linked to better prognosis. Wang et al.⁷⁹ also observed that distinct MCAM(+) fibroblasts in liver metastases may activate CD8 + CXCL13 cells through Notch signaling. Other studies showed that intestinal epithelial Notch1 signaling drives metastasis formation in genomic research¹⁴. This finding suggested a dual role of the Notch pathway in CRC progression and patient survival by regulating immune cells. These studies highlight gene expression differences between primary and metastatic CRC lesions.

Application of transcriptomics in CRLM treatment

Researchers have conducted mRNA expression profiling studies to analyze the correlation between gene expression and therapeutic strategies⁸⁰. Simultaneously, differences in drug sensitivity can be detected at the transcriptomic level, potentially leading to the development of therapeutic agents based on variations in gene expression⁸¹. Transcriptomic sequencing of endothelial cells from CRLM and adjacent normal

liver tissues revealed molecular differences, one of which was upregulation of the checkpoint kinase, WEE1. Subsequent experiments confirmed that WEE1 inhibitors could be promising therapeutic options for the treatment of CRLM⁸². Using single-cell transcriptomic analysis, Zhang et al.⁸³ found that secreted protein acidic and rich in cysteine (SPARC) was significantly upregulated in CRLM. SPARC knockdown reduced CRC cell spheroid and colony formation, invasion, and migration. Sun et al.⁸⁴ analyzed transcriptomic data from primary adjacent tissues, colorectal tumors, and metastases in patients, which revealed that SLITRK4 inhibition suppressed tumor growth and liver metastasis. Pharmacologic inhibition using lipid-polymer hybrid nanoparticles (NPs) to deliver siRNA effectively inhibited CRLM. A transcriptomic analysis is valuable for developing new therapeutic approaches for patients with CRC, with and without liver metastasis. However, current research on the application of transcriptomics in the treatment of liver metastasis is limited.

Application of transcriptomics in the prognostic analysis of CRLM

Transcriptomics and other methods have identified factors that are negatively correlated with CRLM prognosis, as follows:

1. high exosomal CXCL10 expression is linked to poor prognosis and shorter progression-free survival⁸⁵;
2. overexpression of lncRNA-SNHG15 is associated with lower survival rates in patients with CRLM⁸⁶;
3. high miR-221 or miR-222 expression in cancer stroma correlates with liver metastasis, distant metastasis, and short overall survival⁸⁷;
4. miR-200c and miR-196b-5p expression are associated with short overall survival in patients with CRLM⁷⁷;
5. miR-125, miR-127, miR-145, miR-192, miR-194, miR-199-5p, miR-215, and miR-429 expression is associated with poor survival in liver metastases⁸⁸;
6. increased miR-210 and miR-133b expression correlates with reduced survival⁸⁹; and
7. high CIB1 expression is associated with poor progression-free survival and OS⁹⁰.

Additionally, transcriptomic studies have identified the following factors that correlate with CRLM prognosis:

1. low let-7i expression in primary CRC tissues predicts a worse prognosis⁷⁰; and

2. low miR-340 expression is linked to short 5-year disease-free survival and OS⁹¹.

Proteomic studies in CRLM

The concept of a proteome was first proposed by Wilkins et al.⁹² in 1995. A proteome refers to the entire set of proteins expressed in the genome of a cell, tissue, or organism with the respective forms and functional states⁹³. This chapter analyzes the occurrence and progression of liver metastasis in CRC from a proteomic perspective, highlighting the differences between primary colorectal tumors and metastatic liver lesions. We also discuss the implications of proteomic findings in guiding the diagnosis, treatment, and prognosis of CRC.

Proteomic studies on CRLM occurrence and progression

The development and progression of CRC are closely associated with the ECM, which is composed of various proteins, including collagen, proteoglycans, and glycoproteins. Proteomic analyses have identified upregulated collagen types (COL10A1, COL12A1, COL14A1, and COL15A1) in CRLM, which are also present in primary tumors, suggesting ECM alterations involved in tumor proliferation and liver metastasis⁹⁴. In a study involving 3 recurrent liver metastases from 1 patient, Voß et al.⁹⁵ identified 56 upregulated ECM-related proteins in the 3rd metastatic lesion, 26 of which were linked to poor prognosis in CRC. This finding indicated varying malignancy levels in liver metastases.

Epithelial-mesenchymal transition (EMT) is a prerequisite for metastasis. Thrombospondin-1 (THBS1) was shown to promote CRLM by facilitating EMT based on a proteomic analysis of primary CRC specimens⁹⁶. Unstable epithelial/mesenchymal (E/M)-type tumor cells exhibit the strongest potential for liver metastasis. The proportion of E/M-type circulating tumor cells is associated with distant metastasis. Furthermore, EMT-related protein clusters (ERBB2, COL6A1, and CAVIN1) are likely implicated in EMT-mediated metastasis⁹⁷.

Other studies utilizing proteomic approaches have identified key proteins associated with CRC and liver metastasis, including heat shock protein family D member 1 (HSPD1), eukaryotic translation elongation factor 1 gamma, heterogeneous

nuclear ribonucleoprotein A2/B1, fibrinogen beta chain (FGB), Talin 1, adaptor related protein complex 2 subunit alpha 2, serrate RNA effector molecule homolog, apolipoprotein C3, phosphoglucomutase 5⁹⁸, filamin A-interacting protein 1-like (FILIP1L), and plasminogen (PLG)⁹⁹, as well as overexpression of apolipoprotein E¹⁰⁰. However, the relationship between these proteins and CRLM requires further validation.

Overall, studies employing proteomic approaches have unveiled the mechanisms underlying CRLM, which are important for advancing our understanding of the initiation and progression of liver metastasis.

Proteomic differences between CRLM and primary tumors

Retrospective studies have revealed molecular differences between primary and metastatic CRC lesions, including the CAM-EMT, RAS-RAF-MEK, PI3K-AKT-PTEN, TGFBR1/SMAD4, apoptotic, and transcriptional error regulation pathways. These findings suggest that overall protein marker expression profiles may exhibit significant differences¹⁰¹. Farhner et al.¹⁰² compared the proteomes of seven specimens from primary and liver metastatic CRC lesions and revealed several upregulated proteins in liver metastasis, particularly those involved in glucose metabolism, including pyruvate carboxylase, fructose-bisphosphate aldolase B, and fructose-1,6-bisphosphatase 1. Moreover, Kim et al.¹⁰³ performed a proteomic analysis of primary and liver metastatic CRC lesions. Several proteins were significantly upregulated in liver metastases, including SERPINA1, APOA1, ITLN1, DES, DBI, SDHA, and CA1 1, as well as arginase and glutathione S-transferase A3¹⁰⁴. Fahrner et al.¹⁰² discovered that liver metastases exhibit a loss of several structural proteins associated with muscle contraction and cell junction assembly, such as vinculin, synaptopodin, and filamin C, compared to primary lesions. This study highlighted the proteomic differences between primary and metastatic liver CRC, providing insights into the clinical challenges of treating liver metastases.

Application of proteomic analysis in diagnosing CRLM

Some studies have identified CRLM predictive factors using proteomic analyses. For example, immunoproteomic profiling of tumor tissues revealed that OLFM4, CD11b, and ITGA2

are overexpressed in both primary colon tumors and liver metastases, suggesting that OLFM4, CD11b, and ITGA2 are potential CRC biomarkers with autoantigenic properties¹⁰⁵. Additionally, proteomic analysis of urine samples identified the following two promising peptides derived from type I collagen: AGPP(-OH)GEAGKP(-OH)GEQGV(-OH)GDLGAP(-OH)GP; and KGNSGEP(-OH)GAPGSKGDTGAKGEP(-OH)GPVG. This study provided a technical reference for the non-invasive detection of CRLM¹⁰⁶. Similarly, other researchers have found that the combination of collagen-derived urinary AGP peptides and serum CEA levels may significantly improve the detection of patients at high risk of CRLM¹⁰⁷. Furthermore, based on a study of collagen biomarkers in urine, the following two naturally occurring peptides (NOPs) were identified: GPP [collagen α -1(I)]; and GND [collagen α -1(III)]. The development of a molecular model combining these NOPs with CEA has enhanced the sensitivity and specificity of diagnosing high-risk patients for CRLM¹⁰⁸.

Application of proteomic analysis in treating CRLM

Proteomic analysis may aid in identifying effective individualized cancer therapeutic targets. Receptor tyrosine kinases (RTKs), which are cell surface receptors involved in the regulation of key biological pathways, are critical targets for cancer treatment. One study quantified RTKs using proteomics to assess the protein abundance of 21 RTKs and demonstrated significant differences between metastatic and normal liver tissues. RET kinase was the most abundant in non-tumor tissues (approximately 35%), while PGFRB was the most abundant RTK in tumors (approximately 47%)¹⁰⁹, highlighting the potential of RTK as a therapeutic target for tyrosine kinase inhibition. Turtoi et al.¹¹⁰ found that the proteomic characteristics of different regions of CRC liver metastases vary. Among the antigens that can uniformly target the entire liver lesion, LTBP2, and IGFBI are particularly suitable for liver metastasis-targeted therapy. Wertenbroek et al.¹¹¹ conducted thermal ablation treatment (either cryoablation or radiofrequency ablation) in patients with CRC with liver metastases, followed by proteomic analysis. The results indicated that radiofrequency ablation is superior to cryoablation, with longer survival and a lower incidence of complications. Therefore, proteomic-based phenotypic analysis provides valuable support for the localized treatment of CRLM.

Application of proteomic analysis in the prognosis of CRLM

Proteomic analysis has been shown to predict the prognosis of patients with liver metastases. Upregulation of gankyrin (a small molecular protein) is positively correlated with disease progression and liver metastasis in patients with CRC¹¹². Additionally, positive expression of the polymeric immunoglobulin receptor (pIgR) is significantly associated with poor prognosis in patients with CRLM¹¹³. In patients with CRC and liver metastasis, an elevated level of extracellular vesicle protein is significantly correlated with shortened OS both before and after surgery¹¹⁴. Zhu et al.¹¹⁵ developed a decision-tree model using eight proteomic features (m/z 3315, 6637, 1207, 1466, 4167, 4210, 2660, and 4186) and demonstrated the potential value in predicting liver metastasis in patients undergoing radical CRC surgery. Kirana et al.¹¹⁶ showed that the proteins, HLAB, ADAMTS 2, LTBP 3, JAG 2, and NME 2, are significantly associated with tumor progression, vascular invasion, and distant liver metastasis based on differential protein expression analysis. Spatial mapping of the tumor proteome in CRLM revealed that three specific peptides (histone H4, hemoglobin subunit alpha, and inosine-5'-monophosphate dehydrogenase 2) and two unknown m/z values (1305.840 and 1661.060) are significantly elevated in patients with shorter survival. These molecules may serve as potential prognostic biomarkers¹¹⁷.

Overall, proteomic analysis to study CRLM can assist in the diagnosis, treatment, and improvement of prognosis. Proteomics can be used to identify new drug targets, enabling the design of novel therapies targeting the different pathways involved in CRLM.

Applications of metabolomics in the progression, treatment, and prognosis of CRLM

Metabolomics involves qualitative and quantitative analyses of all metabolites within an organism to determine the relationships with physiologic or pathologic changes⁴. Metabolomics can identify potential biomarkers for CRLM, monitor metastatic progression, and assess treatment responses.

Serum metabolomic profiling can serve as a tool for distinguishing different stages of CRC. Notably, serum metabolomic

features differ between patients with locally advanced CRC and patients with liver-only metastases. Furthermore, significant differences in serum metabolomic profiles were observed between patients with liver-only metastases and patients with extrahepatic metastases, indicating that serum metabolomics can be used for cancer staging and guiding treatment strategies¹¹⁸. The literature is replete with studies showing that metabolomics contributes to the non-invasive diagnosis and staging of CRC^{119,120}. However, research on gut metabolomics with liver metastasis is limited and requires further investigation.

Numerous genes contribute to CRC progression through metabolite alterations and targeting these pathways can prolong survival in CRLM. Research has indicated that the EFNB2/EPHB4 axis increases cholesterol levels in CRLM with hypercholesterolemia linked to tumor growth. A high-cholesterol diet significantly shortens survival in mice, whereas blocking the EFNB2/EPHB4 axis extends the OS^{121,122}. Metabolomic analysis suggests that chondroitin sulfate synthase 1 (CHSY1) gene activation promotes CD8+ T cell exhaustion *via* succinate metabolism, leading to liver metastasis. Artemisinin significantly inhibits CHSY1 and combined with anti-PD1 therapy, enhances treatment efficacy¹²³. Aerobic glycolysis, which is a key metabolic pathway in tumor metabolism, alters pyruvate entry into mitochondria, which is targeted in cancer research¹²⁴. Mitochondrial uncouplers, such as niclosamide ethanolamine (NEN) and oxyclozanide, show effective anti-cancer activity in mouse models of metastatic liver tumors¹²⁴.

Metabolomics has also been explored in the treatment of liver metastasis in CRC. Metabolomic analysis of circulating tumor cells (CTCs) derived from CRLM revealed that the metabolite profiles and associated gene expression in CTC-derived metastatic tissue, particularly the specific upregulation of mRNAs involved in metabolic pathways, such as the folate one-carbon pool, folate biosynthesis, and histidine metabolism, differed significantly from those in parental cells. Additionally, tumors and metastatic sites derived from CTCs exhibit significantly higher invasiveness and chemoresistance than tumors and metastatic sites from cell lines. Therefore, identifying different metabolites could provide valuable insight into cancer progression and metastasis, thereby offering potential targets for treating metastatic CRC¹²⁵. Mass spectrometry-based metabolomic analysis was used to characterize the metabolic profile of tumor-associated macrophages (TAMs), which showed that riboflavin is positively correlated with the morphology of larger TAMs (L-TAMs). Riboflavin regulates the expression and activity of lysine-specific demethylase 1A (LSD1) in

L-TAMs and *in vitro* M2-polarized macrophages. The riboflavin-LSD1 axis influences TAM morphology in CRLM, making LSD1 a potential target for reprogramming TAM subtypes and offering new directions for anti-tumor therapy¹²⁶.

Metabolomics is valuable for assessing the prognosis of liver metastases in CRC. Jonas et al.¹²⁷ identified preoperative plasma metabolites, such as lysophosphatidylcholines (lysoPCs) and phosphatidylcholines (PCs), as potential predictors for postoperative disease recurrence in patients with CRLM. Costantini et al.¹²⁸ demonstrated that combined metabolic and lipidomic biomarkers help predict the prognosis of patients with metastatic CRC undergoing liver metastasis resection after induction therapy. Wu et al.¹²⁹ categorized the metabolic phenotypes of CAFs within the TME and showed that scoring this classification could be used to evaluate chemotherapy sensitivity and survival prognosis in patients with liver metastases.

Applications of microbiomics in the diagnosis, treatment, progression, and prognosis of CRLM

Microbiomics focuses on the structure and function of microbial communities, interactions within these communities, and relationships between microbes and their environment or host. Microbiomics also explores regulation of microbial community growth, metabolism, and cooperative processes⁴. The intestinal microbiota significantly contributes to waste degradation, nutrient transport, and gut homeostasis maintenance. Dysbiosis and ecological imbalance in the colon can lead to physiologic disorders¹³⁰, including the development of CRC^{131,132}.

Microbiomics has been extensively explored in the context of pathogenesis, diagnosis, treatment, and prognosis. However, the role of CRLM is the subject of active research. Na et al.¹³³ reported that an increase in *Proteus mirabilis* and a decrease in *Bacteroides vulgatus* significantly influence CRLM, potentially due to a reduction in Kupffer cells in the liver. Studies have shown that cytolethal distending toxin (CDT) produced by *Campylobacter jejuni* promotes CRC metastasis to the liver and lungs *via* the JAK2-STAT3-MMP9 signaling pathway¹³⁴. However, the specific mechanisms linking the gut microbiome to CRLM, as well as potential applications in diagnosing and predicting liver metastasis, require further investigation.

Studies have shown that microbiomics can be applied in treating liver metastasis. Antibiotic therapy is a potential strategy for CRC. Studies have suggested that changes in the oral microbiota

may affect treatment outcomes and prognosis of primary CRC and CRLM radiotherapy. *Fusobacterium nucleatum* (*Fn*) in the oral cavity may migrate and colonize CRC lesions, contributing to radiotherapy resistance. However, combining antibiotics [e.g., metronidazole (MTZ)] can prevent this resistance¹³⁵. *Fn* in CRC liver metastatic tissues correlates with a lower density of CD8(+) T cells and more myeloid-derived suppressor cells. These findings offer critical insights for the development of microbiota- and immune-targeted therapeutic strategies aimed at preventing and treating colorectal cancer metastasis to the liver.¹³⁶ Wang et al.¹³⁷ reported that MTZ inhibits tumor growth and reduces CRLM malignancy by modulating gut *Fn* and altering microbiota composition. Additionally, augmenting the microbiome has potential therapeutic value. Huang et al.¹³⁸ found fecal microbiota transplantation enhances the efficacy of PD-1 blockade in murine models of colorectal cancer. Xu et al.¹³⁹ developed a nanodrug-engineered bacterium (LR-S-CD/CpG@

LNP) in which oral administration of CD/CpG@LNPs induced the production of cytotoxic reactive oxygen species (ROS) at the CRC tumor site through photothermal and photodynamic effects, triggering immunogenic cell death (ICD) in CRC cells. This finding offered a new strategy for oral combination therapy in CRLM. Therefore, gut microbiota transplantation may serve as an adjunctive therapy for advanced CRC, particularly for patients with liver metastasis, by potentially enhancing treatment efficacy through modulation of the TME (**Figure 3**).

Integrated application of multi-omics in the mechanisms, diagnosis, and treatment of CRLM

The integration of multi-omic approaches, including genomics, transcriptomics, epigenomics, microbiomics,

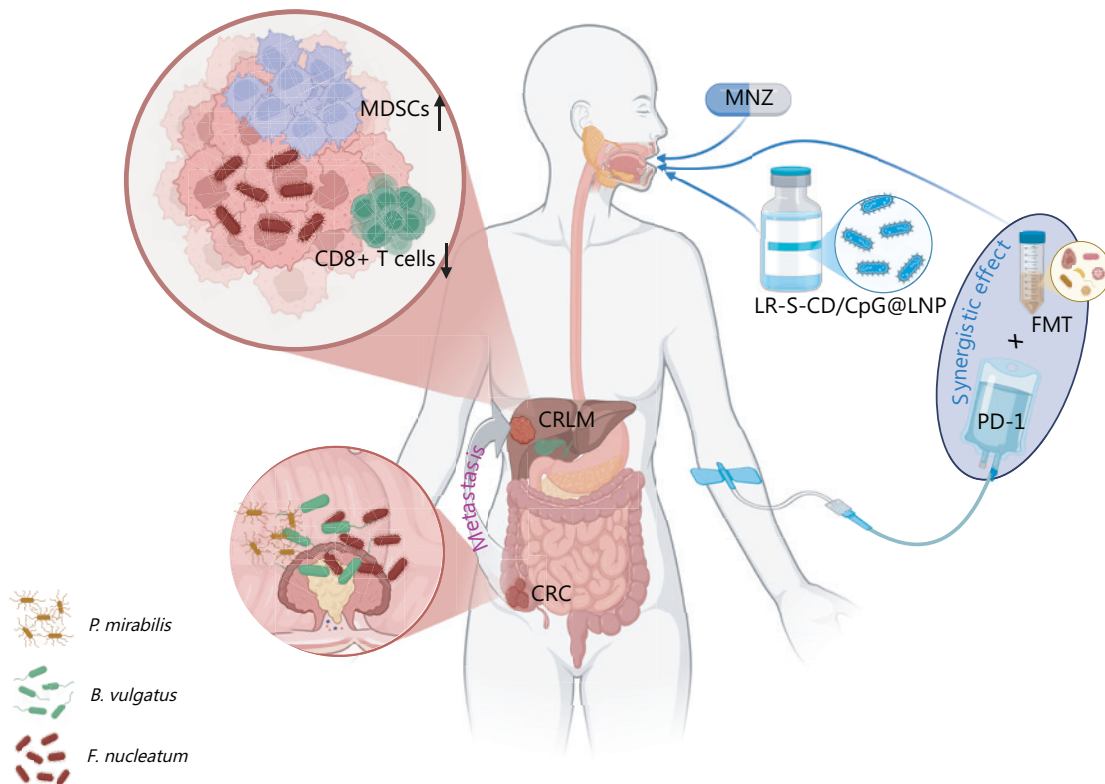


Figure 3 Microbiomics of colorectal cancer liver metastasis (CRLM). Microbiome-related techniques have identified the presence of *Proteus mirabilis*, *Bacteroides vulgatus*, and *Fusobacterium nucleatum* in the primary colorectal cancer (CRC) lesions. *Fusobacterium nucleatum* is also detected within CRLM sites, where its presence is associated with reduced infiltration of CD8+ T cells and increased accumulation of myeloid-derived suppressor cells (MDSCs). Therapeutic approaches, such as oral administration of metronidazole (MNZ) and a nanoengineered probiotic delivery system (LR-S-CD/CpG@LNP), have demonstrated efficacy in treating both primary CRC and CRLM. Fecal microbiota transplantation (FMT) has shown potential to synergize with PD-1 blockade therapy in CRLM.

Multi-omics analysis of colorectal cancer liver metastasis

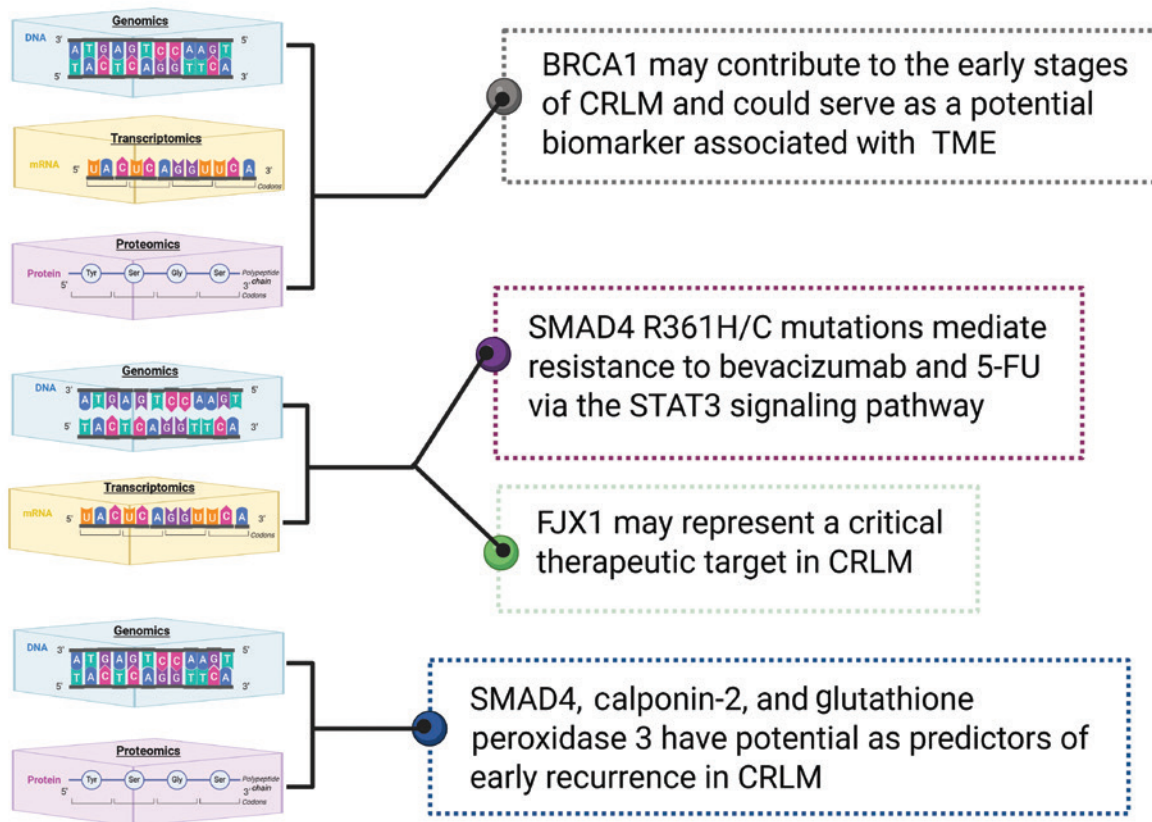


Figure 4 Multi-omics analysis of colorectal cancer liver metastasis (CRLM). Integrated genomic, transcriptomic, and proteomic analyses have suggested a potential role of breast cancer gene 1 (BRCA1) in the early development of CRLM, indicating its promise as a tumor microenvironment (TME)-associated biomarker. Genomic and transcriptomic profiling has identified SMAD family member 4 (SMAD4) R361H/C mutations, which may confer resistance to bevacizumab and 5-fluorouracil (5-FU) via activation of the STAT3 signaling pathway. Four-jointed box 1 (FJX1) is considered to be a potential therapeutic target for CRLM through multi-omics analyses. Combined genomic and proteomic studies have also revealed that SMAD4, calponin-2, and glutathione peroxidase 3 may serve as predictive markers for early recurrence of CRLM.

metabolomics, and proteomics, offers promise for enhancing biomarker sensitivity and addressing population heterogeneity (Figure 4). Chen et al.¹⁴⁰ used genomics, proteomics, and phosphoproteomics to investigate CRC cohorts and found that metastatic tissues are genetically like primary tumors, while significant differences emerged at the proteomic level. Proteomic and phosphoproteomic analyses of primary tumors effectively distinguished metastatic cases with kinase network analysis revealing heterogeneity between primary tumors and liver metastases. Researchers analyzing multi-omics data (genome, epigenome, and transcriptome) from cfDNA and cfRNA samples observed that multi-omics approaches outperformed single-omic data in identifying cancer-associated genes. Additionally, plasma cfRNA was strongly correlated

with tumor RNA for specific cancer- and immune-related features, suggesting that cfRNAs is a non-invasive approach for the clinical monitoring cancer progression and patient status¹⁴¹. Therefore, multi-omics research is crucial for advancing the diagnosis and treatment of CRC.

Numerous studies have used multi-omics approaches to demonstrate the differences and mechanisms underlying primary and metastatic lesions in CRLM. Ham-Karim et al.¹⁰¹ conducted an integrated multi-omics (genomics, transcriptomics, and proteomics) analysis and found that the mutation status of 54 of 60 loci was identical between primary and metastatic tumors, whereas 40 of 58 gene loci exhibited heterogeneity. Furthermore, miRNA expression profiles differed between primary and metastatic tumors. Integrated genomics,

Table 1 Multi-omics summary of colorectal cancer liver metastases

Omic	Characteristics of liver metastases compared to primary lesions	Diagnostic biomarkers	Potential therapeutic targets	Prognostic biomarkers	Ref
Genomics	Genes linked to tissue remodeling and immune response are upregulated, while those associated with proliferation and oxidative phosphorylation are downregulated Mutations are more prevalent; Increased genomic instability	TTE is associated with genetic mutations Genes (<i>NRAS</i> , <i>KRAS</i> , <i>BRAF</i> , <i>PIK3CA</i> , <i>MAPK1</i> , and <i>STAT1</i>) exhibit specific associations with radiomic features	P-cadherin, ANKRD42, oxaliplatin, and mTOR inhibitors	Analyzing fluid specimens with genomic techniques to assess prognosis	8,11-13,17,18,22-24,26
Epigenetics	Downregulation of HIST2H3AK19Ac and overexpression of H2BLK121Ac	TPEF methylation	Reversal of CXCL14 hypermethylation	SLC10A1, MAPT, SHANK2, PTH1R, C2, CAB39, CFLAR, CTSC, THBS1 and TRAPPC3 TNIN12, PAX8, GUF1, KLF4, EVI2B, CEP112, and lncRNA AC011298 TCHH methylation; H3K27me2 and H3K4me2 methylation; histone methylation on circulating nucleosomes (H3K27me3, H4K20me3)	34-37,46,47,50,58,59,63
Transcriptomics	Upregulation of miR-885 and miR-122, downregulation of miR-10b Decreased expression of miR-99b-5p, miR-377, miR-143, miR-10b, miR-28-5p, and miR-200c, and increased expression of miR-196b-5p, miR-122, miR-122*, and miR-885-5p Enrichment of MCAM(+) fibroblasts	Upregulation of circRNA_0001178 and circRNA_0000826	WEE1 inhibitor; SPARC SLITRK4	Exosomal RNA CXCL10 lncRNA-SNHG15; miR-221 or miR-222; CIB1; miRNA let-7i miR-200c and miR-196b-5p; miR-210 and miR-133b; miR-340; miR-429	70,71,73,77,79,82-91
Proteomics	Upregulation of pyruvate carboxylase, fructose-bisphosphate aldolase B, and fructose-1,6-bisphosphatase 1	OLFM4, CD11b, and ITGA2 proteins	RET enzyme and PGFRB kinase	miR-125, miR-127, miR-145, miR-192, miR-194, miR-199-5, miR-215 Gankyrin	102-110,112-114,116,117

Table 1 Continued

Omic	Characteristics of liver metastases compared to primary lesions	Diagnostic biomarkers	Potential therapeutic targets	Prognostic biomarkers	Ref
	Upregulated expression of SERPINA1, APOA1, ITLN1, DES, DBI, SDHA, and CA1	Urinary AGP peptides correlated with serum CEA levels	LTBP2 and IGFB1	pIgR (polymeric immunoglobulin receptor); Extracellular vesicle protein levels; Histone H4, Hemoglobin subunit alpha, and Inosine-5'-monophosphate dehydrogenase 2	
	Upregulated expression of arginase and glutathione S-transferase A3	Type I peptide fragments AGPP(-OH)GEAGKP(-OH) GEQGV(-OH)GDLGAP(-OH)GP and KNGSGEP(-OH) GAPGSKGDTGAKGEP(-OH) GPVG detected in urine		HLAB, ADAMTS2, LTBP3, JAG2, and NME2 proteins	
	Loss of desmin, synaptophysin, and filamin-C	Combination of NOP and CEA			
Metabolomics	The EFN2/EPHB4 axis increases total cholesterol levels in liver metastatic lesions of colorectal cancer		Inhibition of CHSY1 combined with anti-PD1 treatment	Preoperative plasma metabolites, lysophosphatidylcholine (lysoPCs) and phosphatidylcholine (PCs)	121-124,126,127
Microbiomics			Mitochondrial uncouplers nicotinamide ethanalamide (NEN) and hydroxychloroquine	Metabolism-associated phenotypic scoring of CAFs in the tumor microenvironment	
			Metronidazole modulates intestinal <i>Fn</i>	Regulation of the riboflavin-LSD1 axis	135,137-139
			Combination with antibiotics (e.g., MTZ)		
			Fecal microbiota transplantation		
			Nano-drug engineered bacteria (LR-S-CD/CpG@LNP)		

transcriptomics, and proteomics analysis identified *BRCA 1* as 1 of 20 transcripts simultaneously upregulated in all 3 types of TME liver cells during CRLM. The most likely sequence of cellular activation during metastasis involves endothelial (Ito) followed by Kupffer cells. Immunohistochemical analysis of human liver metastases revealed BRCA1 protein co-localization with Ito, Kupffer, and endothelial cells in 81.8% of early or synchronous metastases. This finding suggested that BRCA1 co-expression in these cells may contribute to the early stages of CRLM, thus highlighting the potential of BRCA1 as a TME biomarker¹⁴².

Multi-omics analysis holds promise for elucidating the mechanisms underlying treatment resistance in CRC. Shi et al.¹⁴³ revealed changes in genes and the microenvironment during chemotherapy (bevacizumab combined with chemotherapy) for CRLM based on multi-omics analysis. Shi et al.¹⁴³ found that 92% of cases exhibited minimal change at the genomic level but significant differences at the transcriptomic level. Specifically, the SMAD4 R361H/C mutation mediates resistance to bevacizumab and 5-FU *via* the STAT3 signaling pathway. Combining the STAT3 inhibitor, GB201, with the initial treatment restored the therapeutic sensitivity of SMAD4 R361H/C mutated cancer cells. Thus, multi-omics analysis reveals resistance mechanisms during treatment and enables effective intervention.

Studies on genomics and transcriptomics as prognostic biomarkers for CRLM have shown that CTAG1A, CSTL1, FJX1, IER5L, and KLHL35 expression is higher in metastatic lesions than primary tumors. These genes may contribute to cancer cell metastasis. Specifically, FJX1 mRNA expression is elevated in CRC tissues at various T stages and in metastatic lymph nodes than in normal mucosa or lymphatic tissues. Gene expression analysis suggested that FJX1 regulates chromatin-modifying enzymes, the Notch signaling pathway, cellular senescence, and other signaling pathways. Therefore, FJX1 may be a crucial target for CRLM and a potential novel biomarker for its prediction and treatment¹⁴⁴.

Multi-omics analysis aids in prognosis monitoring for patients with CRLM. Wong et al.¹⁴⁵ used genomics and proteomics to accurately identify patients at risk of early relapse after curative treatment. Wong et al.¹⁴⁵ found the somatic mutations most associated with early relapse were TP53 (88%), APC (71%), KRAS (38%), and SMAD4 (21%). Additionally, proteins associated with early relapse included calponin-2, versican core protein, glutathione peroxidase 3, fibulin-5, and

amyloid- β precursor protein. Further analysis indicated that SMAD4, calponin-2, and glutathione peroxidase 3 may have predictive potential for early relapse, which aids in optimizing prognosis evaluation for CRLM.

Overall, multi-omics data related to tumor cells and tissues provide a more comprehensive understanding of the pathogenesis, diagnostic and therapeutic strategies, drug resistance mechanisms, and prognostic evaluation of the corresponding diseases compared to single-omics data. However, research applying multi-omics approaches to CRLM is limited.

Summary and future directions

Advances in genomics, transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics have paved a solid foundation for precise oncologic research. CRLM is a key factor for poor prognosis in CRC. Applying omics approaches to CRLM can guide the diagnosis, treatment, and prognosis of advanced CRC. This strategy offers more effective management and improved survival outcomes for patients with liver metastasis (Table 1).

Proteomic-related research on CRLM has focused extensively on pathogenesis, diagnosis, metastatic vs. primary tumors, treatment, and prognosis. Future studies should explore clinical translation to provide more therapeutic options for patients with liver metastasis.

Current omics research on CRLM requires further basic studies to explore underlying mechanisms. Genomic studies mostly focus on differences between primary tumors and metastatic sites but miss mechanisms directly linked to liver metastasis onset and therapeutic strategies. Epigenomic research, especially on DNA methylation, lacks studies on treatments for CRLM. Research on histone methylation and demethylation is limited with few studies investigating specific mechanisms. Although transcriptomic studies on CRLM are abundant, progress in improving the diagnosis of liver metastasis is limited. Metabolomics research in CRC mainly targets lipid and gut microbiota metabolites, with few studies on liver metastasis. Microbiological research has focused on CRC initiation and progression, treatment, and prognosis. However, research into the role of the microbiota in CRLM has been minimal. These gaps in knowledge present significant opportunities for further exploration.

Grant support

This study was supported by grants from the Natural Science Foundation of Chongqing (Grant No. CSTB2024NSCQ-MSX0478).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Kexue Zhou, Yan Li.

Collected the data: Kexue Zhou.

Contributed data or analysis tools: Kexue Zhou, Chengxiang Yang.

Performed the analysis: Kexue Zhou, Yan Li.

Wrote the paper: Kexue Zhou.

References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024; 74: 229-63.
- Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg.* 2006; 244: 254-9.
- Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart A. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. *J Clin Oncol.* 2010; 28: 256-63.
- Zhao J, Yang J. Multi-omics research for precision medicine. Beijing: Science Press; 2021.
- Ki DH, Jeung HC, Park CH, Kang SH, Lee GY, Lee WS, et al. Whole genome analysis for liver metastasis gene signatures in colorectal cancer. *Int J Cancer.* 2007; 121: 2005-12.
- Yamasaki M, Takemasa I, Komori T, Watanabe S, Sekimoto M, Doki Y, et al. The gene expression profile represents the molecular nature of liver metastasis in colorectal cancer. *Int J Oncol.* 2007; 30: 129-38.
- Wang HW, Yan XL, Wang LJ, Zhang MH, Yang CH, Wei L, et al. Characterization of genomic alterations in Chinese colorectal cancer patients with liver metastases. *J Transl Med.* 2021; 19: 313.
- Lin HM, Chatterjee A, Lin YH, Anjomshoaa A, Fukuzawa R, McCall JL, et al. Genome wide expression profiling identifies genes associated with colorectal liver metastasis. *Oncol Rep.* 2007; 17: 1541-9.
- Shiomi A, Kusuvara M, Sugino T, Sugiura T, Ohshima K, Nagashima T, et al. Comprehensive genomic analysis contrasting primary colorectal cancer and matched liver metastases. *Oncol Lett.* 2021; 21: 466.
- Hu CT, Wang JL, Hou T, Yan ZW, Zu LD, Fu GH, et al. Comprehensive mutation profiling of colorectal cancer patients with lung or liver metastasis by targeted next-generation sequencing. *Technol Cancer Res Treat.* 2023; 22: 15330338231185285.
- Diep CB, Parada LA, Teixeira MR, Eknaes M, Nesland JM, Johansson B, et al. Genetic profiling of colorectal cancer liver metastases by combined comparative genomic hybridization and G-banding analysis. *Genes Chromosomes Cancer.* 2003; 36: 189-97.
- Sayagués JM, Corchete LA, Gutiérrez ML, Sarasquete ME, Del Mar Abad M, Bengoechea O, et al. Genomic characterization of liver metastases from colorectal cancer patients. *Oncotarget.* 2016; 7: 72908-22.
- Muñoz-Bellvis L, Fontanillo C, González-González M, García E, Iglesias M, Esteban C, et al. Unique genetic profile of sporadic colorectal cancer liver metastasis versus primary tumors as defined by high-density single-nucleotide polymorphism arrays. *Mod Pathol.* 2012; 25: 590-601.
- Jackstadt R, van Hooff SR, Leach JD, Cortes-Lavaud X, Lohuis JO, Ridgway RA, et al. Epithelial NOTCH signaling rewires the tumor microenvironment of colorectal cancer to drive poor-prognosis subtypes and metastasis. *Cancer Cell.* 2019; 36: 319-36.e7.
- Sathe A, Mason K, Grimes SM, Zhou Z, Lau BT, Bai X, et al. Colorectal cancer metastases in the liver establish immunosuppressive spatial networking between tumor-associated SPP1+ macrophages and fibroblasts. *Clin Cancer Res.* 2023; 29: 244-60.
- Rong D, Sun G, Zheng Z, Liu L, Chen X, Wu F, et al. MGP promotes CD8⁺ T cell exhaustion by activating the NF-κB pathway leading to liver metastasis of colorectal cancer. *Int J Biol Sci.* 2022; 18: 2345-61.
- Seth A, Amemiya Y, Cheung H, Hsieh E, Law C, Milot L. Delayed MRI enhancement of colorectal cancer liver metastases is associated with metastatic mutational profile. *Cancer Genomics Proteomics.* 2021; 18: 627-35.
- Wang X, Li N, Guo H, Yin X, Zheng Y. Correlation analysis of gene and radiomic features in colorectal cancer liver metastases. *Comput Math Methods Med.* 2022; 2022: 8559011.
- Margonis GA, Sasaki K, Kim Y, Samaha M, Buettner S, Amini N, et al. Tumor biology rather than surgical technique dictates prognosis in colorectal cancer liver metastases. *J Gastrointest Surg.* 2016; 20: 1821-9.
- Chan AKC, Mason JM, Baltatzis M, Siriwardena AK. Management of colorectal cancer with synchronous liver metastases: an inception cohort study (CoSMIC). *Ann Surg Oncol.* 2022; 29: 1939-51.
- Brudvik KW, Shindoh J. Limitations of molecular biomarkers in patients with resectable colorectal liver metastases. *Chin Clin Oncol.* 2019; 8: 48.

22. Sun L, Hu H, Peng L, Zhou Z, Zhao X, Pan J, et al. P-cadherin promotes liver metastasis and is associated with poor prognosis in colon cancer. *Am J Pathol.* 2011; 179: 380-90.
23. Liu S, Zhang Z, Wang Z, Li J, Shen L. Genome-wide CRISPR screening identifies the pivotal role of ANKRD42 in colorectal cancer metastasis through EMT regulation. *IUBMB Life.* 2024; 76: 803-19.
24. Lu M, Zessin AS, Glover W, Hsu DS. Activation of the mTOR pathway by oxaliplatin in the treatment of colorectal cancer liver metastasis. *PLoS One.* 2017; 12: e0169439.
25. Alves JM, Prado-López S, Tomás L, Valecha M, Estévez-Gómez N, Alvariño P, et al. Clonality and timing of relapsing colorectal cancer metastasis revealed through whole-genome single-cell sequencing. *Cancer Lett.* 2022; 543: 215767.
26. Bolhuis K, van 't Erve I, Mijns C, Delis-Van Diemen PM, Huisken J, Komurcu A, et al. Postoperative circulating tumour DNA is associated with pathologic response and recurrence-free survival after resection of colorectal cancer liver metastases. *EBioMedicine.* 2021; 70: 103498.
27. Wang D, Liu B, Zhang Z. Accelerating the understanding of cancer biology through the lens of genomics. *Cell.* 2023; 186: 1755-71.
28. Weichenhan D, Lipka DB, Lutsik P, Goyal A, Plass C. Epigenomic technologies for precision oncology. *Semin Cancer Biol.* 2022; 84: 60-8.
29. Patel SA, Vanharanta S. Epigenetic determinants of metastasis. *Mol Oncol.* 2017; 11: 79-96.
30. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. *N Engl J Med.* 2003; 349: 2042-54.
31. Weber M, Hellmann I, Stadler MB, Ramos L, Pääbo S, Rebhan M, et al. Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. *Nat Genet.* 2007; 39: 457-66.
32. Antequera F, Bird A. Number of CpG islands and genes in human and mouse. *Proc Natl Acad Sci U S A.* 1993; 90: 11995-9.
33. Zhang C, Wang L, Jin C, Zhou J, Peng C, Wang Y, et al. Long non-coding RNA Lnc-LALC facilitates colorectal cancer liver metastasis via epigenetically silencing LZTS1. *Cell Death Dis.* 2021; 12: 224.
34. Liu J, Li H, Sun L, Shen S, Zhou Q, Yuan Y, et al. Epigenetic alternations of microRNAs and DNA methylation contribute to liver metastasis of colorectal cancer. *Dig Dis Sci.* 2019; 64: 1523-34.
35. Li W, Guo L, Tang W, Ma Y, Wang X, Shao Y, et al. Identification of DNA methylation biomarkers for risk of liver metastasis in early-stage colorectal cancer. *Clin Epigenetics.* 2021; 13: 126.
36. Gai W, Ji L, Lam WKJ, Sun K, Jiang P, Chan AWH, et al. Liver- and colon-specific DNA methylation markers in plasma for investigation of colorectal cancers with or without liver metastases. *Clin Chem.* 2018; 64: 1239-49.
37. Ebert MP, Mooney SH, Tonnes-Priddy L, Lograsso J, Hoffmann J, Chen J, et al. Hypermethylation of the TPEF/HPP1 gene in primary and metastatic colorectal cancers. *Neoplasia.* 2005; 7: 771-8.
38. Ebert MP, Model F, Mooney S, Hale K, Lograsso J, Tonnes-Priddy L, et al. Aristaless-like homeobox-4 gene methylation is a potential marker for colorectal adenocarcinomas. *Gastroenterology.* 2006; 131: 1418-30.
39. Hanski C, Riede E, Gratchev A, Foss HD, Böhm C, Klussmann E, et al. MUC2 gene suppression in human colorectal carcinomas and their metastases: in vitro evidence of the modulatory role of DNA methylation. *Lab Invest.* 1997; 77: 685-95.
40. Lu CH, Wu WY, Lai YJ, Yang CM, Yu LC. Suppression of B3GNT7 gene expression in colon adenocarcinoma and its potential effect in the metastasis of colon cancer cells. *Glycobiology.* 2014; 24: 359-67.
41. Tommasi S, Pinto R, Petriella D, Pilato B, Lacalamita R, Santini D, et al. Oncosuppressor methylation: a possible key role in colon metastatic progression. *J Cell Physiol.* 2011; 226: 1934-9.
42. Ju HX, An B, Okamoto Y, Shinjo K, Kanemitsu Y, Komori K, et al. Distinct profiles of epigenetic evolution between colorectal cancers with and without metastasis. *Am J Pathol.* 2011; 178: 1835-46.
43. Rodger EJ, Gimenez G, Ajithkumar P, Stockwell PA, Almomani S, Bowden SA, et al. An epigenetic signature of advanced colorectal cancer metastasis. *iScience.* 2023; 26: 106986.
44. Orjuela S, Menigatti M, Schraml P, Kambakamba P, Robinson MD, Marra G. The DNA hypermethylation phenotype of colorectal cancer liver metastases resembles that of the primary colorectal cancers. *BMC Cancer.* 2020; 20: 290.
45. Pulverer W, Kruusmaa K, Schöthaler S, Huber J, Bitenc M, Bachleitner-Hofmann T, et al. Multiplexed DNA methylation analysis in colorectal cancer using liquid biopsy and its diagnostic and predictive value. *Curr Issues Mol Biol.* 2021; 43: 1419-35.
46. Chen S, Liu T, Bu D, Zhu J, Wang X, Pan Y, et al. Methylome profiling identifies TCHH methylation in CfDNA as a noninvasive marker of liver metastasis in colorectal cancer. *FASEB J.* 2021; 35: e21720.
47. Wang Y, Wang S, Niu Y, Ma B, Li J. Data mining suggests that CXCL14 gene silencing in colon cancer is due to promoter methylation. *Int J Mol Sci.* 2023; 24: 16027.
48. Tan M, Luo H, Lee S, Jin F, Yang JS, Montellier E, et al. Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. *Cell.* 2011; 146: 1016-28.
49. Kouzarides T. Chromatin modifications and their function. *Cell.* 2007; 128: 693-705.
50. Tamagawa H, Oshima T, Shiozawa M, Morinaga S, Nakamura Y, Yoshihara M, et al. The global histone modification pattern correlates with overall survival in metachronous liver metastasis of colorectal cancer. *Oncol Rep.* 2012; 27: 637-42.
51. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. *Nat Rev Genet.* 2012; 13: 343-57.
52. Ruthenburg AJ, Allis CD, Wysocka J. Methylation of lysine 4 on histone H3: intricacy of writing and reading a single epigenetic mark. *Mol Cell.* 2007; 25: 15-30.
53. Klose RJ, Zhang Y. Regulation of histone methylation by demethylimination and demethylation. *Nat Rev Mol Cell Biol.* 2007; 8: 307-18.
54. Kouzarides T. Histone methylation in transcriptional control. *Curr Opin Genet Dev.* 2002; 12: 198-209.
55. Boonsanay V, Mosa MH, Looso M, Weichenhan D, Ceteci F, Pudielko L, et al. Loss of SUV420H2-dependent chromatin compaction drives right-sided colon cancer progression. *Gastroenterology.* 2023; 164: 214-27.

56. Chen X, Xu M, Xu X, Zeng K, Liu X, Pan B, et al. METTL14-mediated N6-methyladenosine modification of SOX4 mrna inhibits tumor metastasis in colorectal cancer. *Mol Cancer*. 2020; 19: 106.
57. Ding J, Zhang ZM, Xia Y, Liao GQ, Pan Y, Liu S, et al. LSD1-mediated epigenetic modification contributes to proliferation and metastasis of colon cancer. *Br J Cancer*. 2013; 109: 994-1003.
58. Tamagawa H, Oshima T, Numata M, Yamamoto N, Shiozawa M, Morinaga S, et al. Global histone modification of H3K27 correlates with the outcomes in patients with metachronous liver metastasis of colorectal cancer. *Eur J Surg Oncol*. 2013; 39: 655-61.
59. Gezer U, Yörüker EE, Keskin M, Kulle CB, Dharuman Y, Holdenrieder S. Histone methylation marks on circulating nucleosomes as novel blood-based biomarker in colorectal cancer. *Int J Mol Sci*. 2015; 16: 29654-62.
60. Kang KA, Piao MJ, Ryu YS, Kang HK, Chang WY, Keum YS, et al. Interaction of DNA demethylase and histone methyltransferase upregulates Nrf2 in 5-fluorouracil-resistant colon cancer cells. *Oncotarget*. 2016; 7: 40594-620.
61. Sasidharan Nair V, Toor SM, Taha RZ, Shaath H, Elkord E. DNA methylation and repressive histones in the promoters of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, PD-L1, and galectin-9 genes in human colorectal cancer. *Clin Epigenetics*. 2018; 10: 104.
62. Zhang Y, Sun Z, Jia J, Du T, Zhang N, Tang Y, et al. Overview of histone modification. *Adv Exp Med Biol*. 2021; 1283: 1-16.
63. Shen Z, Wang B, Luo J, Jiang K, Zhang H, Mustonen H, et al. Global-scale profiling of differential expressed lysine acetylated proteins in colorectal cancer tumors and paired liver metastases. *J Proteomics*. 2016; 142: 24-32.
64. Deng Y, Gao J, Xu G, Yao Y, Sun Y, Shi Y, et al. HDAC6-dependent deacetylation of AKAP12 dictates its ubiquitination and promotes colon cancer metastasis. *Cancer Lett*. 2022; 549: 215911.
65. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet*. 2009; 10: 57-63.
66. Sha Z, Gao Q, Wang L, An N, Wu Y, Wei D, et al. Investigating the cell origin and liver metastasis factors of colorectal cancer by single-cell transcriptome analysis. *Onco Targets Ther*. 2024; 17: 345-58.
67. Li C, Xu J, Wang X, Zhang C, Yu Z, Liu J, et al. Whole exome and transcriptome sequencing reveal clonal evolution and exhibit immune-related features in metastatic colorectal tumors. *Cell Death Discov*. 2021; 7: 222.
68. Teng S, Li YE, Yang M, Qi R, Huang Y, Wang Q, et al. Tissue-specific transcription reprogramming promotes liver metastasis of colorectal cancer. *Cell Res*. 2020; 30: 34-49.
69. Cai J, Zhang W, Lu Y, Liu W, Zhou H, Liu M, et al. Single-cell exome sequencing reveals polyclonal seeding and TRPS1 mutations in colon cancer metastasis. *Signal Transduct Target Ther*. 2024; 9: 247.
70. Hur K, Toiyama Y, Schetter AJ, Okugawa Y, Harris CC, Boland CR, et al. Identification of a metastasis-specific microRNA signature in human colorectal cancer. *J Natl Cancer Inst*. 2015; 107: dju492.
71. Vychytilova-Faltejskova P, Pesta M, Radova L, Liska V, Daum O, Kala Z, et al. Genome-wide microRNA expression profiling in primary tumors and matched liver metastasis of patients with colorectal cancer. *Cancer Genomics Proteomics*. 2016; 13: 311-6.
72. Makondi PT, Wei PL, Huang CY, Chang YJ. Development of novel predictive miRNA/target gene pathways for colorectal cancer distance metastasis to the liver using a bioinformatic approach. *PLoS One*. 2019; 14: e0211968.
73. Xu H, Wang C, Song H, Xu Y, Ji G. RNA-Seq profiling of circular RNAs in human colorectal cancer liver metastasis and the potential biomarkers. *Mol Cancer*. 2019; 18: 8.
74. Fleischer JR, Schmitt AM, Haas G, Xu X, Zeisberg EM, Bohnenberger H, et al. Molecular differences of angiogenic versus vessel co-opting colorectal cancer liver metastases at single-cell resolution. *Mol Cancer*. 2023; 22: 17.
75. Li X, Pan J, Liu T, Yin W, Miao Q, Zhao Z, et al. Novel TCF21^{high} pericyte subpopulation promotes colorectal cancer metastasis by remodelling perivascular matrix. *Gut*. 2023; 72: 710-21.
76. Rada M, Kapelanski-Lamoureux A, Petrillo S, Tabariès S, Siegel P, Reynolds AR, et al. Runt related transcription factor-1 plays a central role in vessel co-option of colorectal cancer liver metastases. *Commun Biol*. 2021; 4: 950.
77. Li W, Chang J, Tong D, Peng J, Huang D, Guo W, et al. Differential microRNA expression profiling in primary tumors and matched liver metastasis of patients with colorectal cancer. *Oncotarget*. 2017; 8: 35783-91.
78. Kong H, Wu Y, Zhu M, Zhai C, Qian J, Gao X, et al. Long non-coding RNAs: novel prognostic biomarkers for liver metastases in patients with early stage colorectal cancer. *Oncotarget*. 2016; 7: 50428-36.
79. Wang F, Long J, Li L, Wu ZX, Da TT, Wang XQ, et al. Single-cell and spatial transcriptome analysis reveals the cellular heterogeneity of liver metastatic colorectal cancer. *Sci Adv*. 2023; 9: eadf5464.
80. Ji D, Song C, Li Y, Xia J, Wu Y, Jia J, et al. Combination of radiotherapy and suppression of tregs enhances abscopal antitumor effect and inhibits metastasis in rectal cancer. *J Immunother Cancer*. 2020; 8: e000826.
81. Bruun J, Kryeziu K, Eide PW, Moosavi SH, Eilertsen IA, Langerud J, et al. Patient-derived organoids from multiple colorectal cancer liver metastases reveal moderate intra-patient pharmacotranscriptomic heterogeneity. *Clin Cancer Res*. 2020; 26: 4107-19.
82. Webster PJ, Littlejohns AT, Gaunt HJ, Young RS, Rode B, Ritchie JE, et al. Upregulated WEE1 protects endothelial cells of colorectal cancer liver metastases. *Oncotarget*. 2017; 8: 42288-99.
83. Zhang H, Zhuo C, Lin R, Ke F, Wang M, Yang C. Identification and verification of key genes in colorectal cancer liver metastases through analysis of single-cell sequencing data and TCGA data. *Ann Surg Oncol*. 2024; 31: 8664-79.
84. Sun X, Zhang J, Dong B, Xiong Q, Wang X, Gu Y, et al. Targeting SLITRK4 restrains proliferation and liver metastasis in colorectal cancer via regulating PI3K/AKT/NFκB pathway and tumor-associated macrophage. *Adv Sci (Weinh)*. 2025; 12: e2400367.
85. Lee S, Park YS, Kim JH, Lim AR, Hyun MH, Kim B, et al. Identification of biomarkers associated with liver metastasis

- progression from colorectal cancer using exosomal RNA profiling. *Cancers (Basel)*. 2022; 14: 4723.
86. Huang L, Lin H, Kang L, Huang P, Huang J, Cai J, et al. Aberrant expression of long noncoding RNA SNHG15 correlates with liver metastasis and poor survival in colorectal cancer. *J Cell Physiol*. 2019; 234: 7032-9.
 87. Iida M, Hazama S, Tsunedomi R, Tanaka H, Takenouchi H, Kanekiyo S, et al. Overexpression of miR-221 and miR-222 in the cancer stroma is associated with malignant potential in colorectal cancer. *Oncol Rep*. 2018; 40: 1621-31.
 88. Pecqueux M, Liebetrau I, Werft W, Dienemann H, Muley T, Pfannschmidt J, et al. A comprehensive microRNA expression profile of liver and lung metastases of colorectal cancer with their corresponding host tissue and its prognostic impact on survival. *Int J Mol Sci*. 2016; 17: 1755.
 89. Ellermeier C, Vang S, Cleveland K, Durand W, Resnick MB, Brodsky AS. Prognostic microRNA expression signature from examination of colorectal primary and metastatic tumors. *Anticancer Res*. 2014; 34: 3957-67.
 90. Fan S, Fleischer JR, Dokshokova L, Böhme LS, Haas G, Schmitt AM, et al. High CIB1 expression in colorectal cancer liver metastases correlates with worse survival and the replacement histopathological growth pattern. *Mol Ther Oncol*. 2024; 32: 200828.
 91. Takeyama H, Yamamoto H, Yamashita S, Wu X, Takahashi H, Nishimura J, et al. Decreased miR-340 expression in bone marrow is associated with liver metastasis of colorectal cancer. *Mol Cancer Ther*. 2014; 13: 976-85.
 92. Wasinger VC, Cordwell SJ, Cerpa-Poljak A, Yan JX, Gooley AA, Wilkins MR, et al. Progress with gene-product mapping of the *Mollicutes: mycoplasma genitalium*. *Electrophoresis*. 1995; 16: 1090-4.
 93. The promise of proteomics. *Nature*. 1999; 402: 703.
 94. van Huizen NA, Coebergh van den Braak RRJ, Doukas M, Dekker LJM, IJzermans JNM, Luidert TM. Up-regulation of collagen proteins in colorectal liver metastasis compared with normal liver tissue. *J Biol Chem*. 2019; 294: 281-9.
 95. Voß H, Wurlitzer M, Smit DJ, Ewald F, Alawi M, Spohn M, et al. Differential regulation of extracellular matrix proteins in three recurrent liver metastases of a single patient with colorectal cancer. *Clin Exp Metastasis*. 2020; 37: 649-56.
 96. Liu X, Xu D, Liu Z, Li Y, Zhang C, Gong Y, et al. THBS1 facilitates colorectal liver metastasis through enhancing epithelial-mesenchymal transition. *Clin Transl Oncol*. 2020; 22: 1730-40.
 97. Huang MS, Fu LH, Yan HC, Cheng LY, Ru HM, Mo S, et al. Proteomics and liquid biopsy characterization of human EMT-related metastasis in colorectal cancer. *Front Oncol*. 2022; 12: 790096.
 98. Yang W, Shi J, Zhou Y, Liu T, Li J, Hong F, et al. Co-expression network analysis identified key proteins in association with hepatic metastatic colorectal cancer. *Proteomics Clin Appl*. 2019; 13: e1900017.
 99. Ku X, Xu Y, Cai C, Yang Y, Cui L, Yan W. In-depth characterization of mass spectrometry-based proteomic profiles revealed novel signature proteins associated with liver metastatic colorectal cancers. *Anal Cell Pathol (Amst)*. 2019; 2019: 7653230.
 100. Zhao Z, Zou S, Guan X, Wang M, Jiang Z, Liu Z, et al. *Apolipoprotein E* overexpression is associated with tumor progression and poor survival in colorectal cancer. *Front Genet*. 2018; 9: 650.
 101. Ham-Karim H, Negm O, Ahmad N, Ilyas M. Investigating genomic, proteomic, and post-transcriptional regulation profiles in colorectal cancer: a comparative study between primary tumors and associated metastases. *Cancer Cell Int*. 2023; 23: 192.
 102. Fahrner M, Bronsert P, Fichtner-Feigl S, Jud A, Schilling O. Proteome biology of primary colorectal carcinoma and corresponding liver metastases. *Neoplasia*. 2021; 23: 1240-51.
 103. Kim EK, Song MJ, Jung Y, Lee WS, Jang HH. Proteomic analysis of primary colon cancer and synchronous solitary liver metastasis. *Cancer Genomics Proteomics*. 2019; 16: 583-92.
 104. Bai X, Li SY, An P, Yu B, Cai HY. Proteome study of colorectal cancer genesis and hepatic metastasis. *Zhonghua Yi Xue Za Zhi*. 2005; 85: 2128-31.
 105. Yang Q, Bavi P, Wang JY, Roehrl MH. Immuno-proteomic discovery of tumor tissue autoantigens identifies olfactomedin 4, CD11b, and integrin alpha-2 as markers of colorectal cancer with liver metastases. *J Proteomics*. 2017; 168: 53-65.
 106. Bröker ME, Lalmahomed ZS, Roest HP, van Huizen NA, Dekker LJ, Calame W, et al. Collagen peptides in urine: a new promising biomarker for the detection of colorectal liver metastases. *PLoS One*. 2013; 8: e70918.
 107. Lalmahomed ZS, Bröker ME, van Huizen NA, Coebergh van den Braak RR, Dekker LJ, Rizopoulos D, et al. Hydroxylated collagen peptide in urine as biomarker for detecting colorectal liver metastases. *Am J Cancer Res*. 2016; 6: 321-30.
 108. van Huizen NA, van Rosmalen J, Dekker LJM, Coebergh van den Braak RRJ, Verhoef C, IJzermans JNM, et al. Identification of a collagen marker in urine improves the detection of colorectal liver metastases. *J Proteome Res*. 2020; 19: 153-60.
 109. Vasilogianni AM, Al-Majdoub ZM, Achour B, Peters SA, Rostami-Hodjegan A, Barber J. Proteomic quantification of receptor tyrosine kinases involved in the development and progression of colorectal cancer liver metastasis. *Front Oncol*. 2023; 13: 1010563.
 110. Turtoi A, Blomme A, Debois D, Somja J, Delvaux D, Patsos G, et al. Organized proteomic heterogeneity in colorectal cancer liver metastases and implications for therapies. *Hepatology*. 2014; 59: 924-34.
 111. Wertenbroek MW, Schepers M, Kamminga-Rasker HJ, Bottema JT, Muller Kobold AC, Roelofs H, et al. Clinical outcome, proteome kinetics and angiogenic factors in serum after thermoablation of colorectal liver metastases. *BMC Cancer*. 2013; 13: 266.
 112. Wang C, Li X, Ren L, Ma C, Wu M, Liang W, et al. Gankyrin as potential biomarker for colorectal cancer with occult liver metastases. *Front Oncol*. 2021; 11: 656852.
 113. Liu F, Ye P, Bi T, Teng L, Xiang C, Wang H, et al. COLORECTAL polymeric immunoglobulin receptor expression is correlated with hepatic metastasis and poor prognosis in colon carcinoma patients with hepatic metastasis. *Hepatogastroenterology*. 2014; 61: 652-9.

114. Lin K, Baenke F, Lai X, Schneider M, Helm D, Polster H, et al. Comprehensive proteomic profiling of serum extracellular vesicles in patients with colorectal liver metastases identifies a signature for non-invasive risk stratification and early-response evaluation. *Mol Cancer*. 2022; 21: 91.
115. Zhu D, Zhong Y, Wu H, Ye L, Wang J, Li Y, et al. Predicting metachronous liver metastasis from colorectal cancer using serum proteomic fingerprinting. *J Surg Res*. 2013; 184: 861-6.
116. Kirana C, Peng L, Miller R, Keating JP, Glenn C, Shi H, et al. Combination of laser microdissection, 2D-DIGE and MALDI-TOF MS to identify protein biomarkers to predict colorectal cancer spread. *Clin Proteomics*. 2019; 16: 3.
117. Li CMY, Briggs MT, Lee YR, Tin T, Young C, Pierides J, et al. Use of tryptic peptide MALDI mass spectrometry imaging to identify the spatial proteomic landscape of colorectal cancer liver metastases. *Clin Exp Med*. 2024; 24: 53.
118. Farshidfar F, Weljie AM, Kopciuk K, Buie WD, Maclean A, Dixon E, et al. Serum metabolomic profile as a means to distinguish stage of colorectal cancer. *Genome Med*. 2012; 4: 42.
119. Coker OO, Liu C, Wu WKK, Wong SH, Jia W, Sung JJY, et al. Altered gut metabolites and microbiota interactions are implicated in colorectal carcinogenesis and can be non-invasive diagnostic biomarkers. *Microbiome*. 2022; 10: 35.
120. Kim M, Vogtmann E, Ahlquist DA, Devens ME, Kisiel JB, Taylor WR, et al. Fecal metabolomic signatures in colorectal adenoma patients are associated with gut microbiota and early events of colorectal cancer pathogenesis. *mBio*. 2020; 11: e03186-19.
121. Liu W, Chakraborty B, Safi R, Kazmin D, Chang CY, McDonnell DP. Dysregulated cholesterol homeostasis results in resistance to ferroptosis increasing tumorigenicity and metastasis in cancer. *Nat Commun*. 2021; 12: 5103.
122. Xu C, Gu L, Kuerbanjiang M, Jiang C, Hu L, Liu Y, et al. Adaptive activation of EFNB2/EPHB4 axis promotes post-metastatic growth of colorectal cancer liver metastases by LDLR-mediated cholesterol uptake. *Oncogene*. 2023; 42: 99-112.
123. Sun G, Zhao S, Fan Z, Wang Y, Liu H, Cao H, et al. CHSY1 promotes CD8⁺ T cell exhaustion through activation of succinate metabolism pathway leading to colorectal cancer liver metastasis based on CRISPR/CAS9 screening. *J Exp Clin Cancer Res*. 2023; 42: 248.
124. Alasadi A, Chen M, Swapna GVT, Tao H, Guo J, Collantes J, et al. Effect of mitochondrial uncouplers niclosamide ethanolamine (NEN) and oxytocinamide on hepatic metastasis of colon cancer. *Cell Death Dis*. 2018; 9: 215.
125. Li M, Wu S, Zhuang C, Shi C, Gu L, Wang P, et al. Metabolomic analysis of circulating tumor cells derived liver metastasis of colorectal cancer. *Heliyon*. 2023; 9: e12515.
126. Soldani C, De Simone G, Polidoro MA, Morabito A, Franceschini B, Colombo FS, et al. Riboflavin-LSD1 axis participates in the in vivo tumor-associated macrophage morphology in human colorectal liver metastases. *Cancer Immunol Immunother*. 2024; 73: 63.
127. Jonas JP, Hackl H, Pereyra D, Santol J, Ortmayr G, Rumpf B, et al. Circulating metabolites as a concept beyond tumor biology determining disease recurrence after resection of colorectal liver metastasis. *HPB (Oxford)*. 2022; 24: 116-29.
128. Costantini S, Di Gennaro E, Capone F, De Stefano A, Nasti G, Vitagliano C, et al. Plasma metabolomics, lipidomics and cytokinomics profiling predict disease recurrence in metastatic colorectal cancer patients undergoing liver resection. *Front Oncol*. 2022; 12: 1110104.
129. Wu C, Yu S, Wang Y, Gao Y, Xie X, Zhang J. Metabolic-suppressed cancer-associated fibroblasts limit the immune environment and survival in colorectal cancer with liver metastasis. *Front Pharmacol*. 2023; 14: 1212420.
130. Thomas S, Izard J, Walsh E, Batich K, Chongsathidkiet P, Clarke G, et al. The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. *Cancer Res*. 2017; 77: 1783-812.
131. Nakatsu G, Li X, Zhou H, Sheng J, Wong SH, Wu WK, et al. Gut mucosal microbiome across stages of colorectal carcinogenesis. *Nat Commun*. 2015; 6: 8727.
132. Kwong TNY, Wang X, Nakatsu G, Chow TC, Tipoe T, Dai RZW, et al. Association between bacteremia from specific microbes and subsequent diagnosis of colorectal cancer. *Gastroenterology*. 2018; 155: 383-90.e8.
133. Yuan N, Li X, Wang M, Zhang Z, Qiao L, Gao Y, et al. Gut microbiota alteration influences colorectal cancer metastasis to the liver by remodeling the liver immune microenvironment. *Gut Liver*. 2022; 16: 575-88.
134. He Z, Yu J, Gong J, Wu J, Zong X, Luo Z, et al. Campylobacter jejuni-derived cytolethal distending toxin promotes colorectal cancer metastasis. *Cell Host Microbe*. 2024; 32: 2080-91.e6.
135. Dong J, Li Y, Xiao H, Zhang S, Wang B, Wang H, et al. Oral microbiota affects the efficacy and prognosis of radiotherapy for colorectal cancer in mouse models. *Cell Rep*. 2021; 37: 109886.
136. Sakamoto Y, Mima K, Ishimoto T, Ogata Y, Imai K, Miyamoto Y, et al. Relationship between fusobacterium nucleatum and antitumor immunity in colorectal cancer liver metastasis. *Cancer Sci*. 2021; 112: 4470-7.
137. Wang M, Li Y, Yang X, Liu Z, Wang K, Gong D, et al. Effects of metronidazole on colorectal cancer occurrence and colorectal cancer liver metastases by regulating Fusobacterium nucleatum in mice. *Immun Inflamm Dis*. 2023; 11: e1067.
138. Huang J, Zheng X, Kang W, Hao H, Mao Y, Zhang H, et al. Metagenomic and metabolomic analyses reveal synergistic effects of fecal microbiota transplantation and anti-PD-1 therapy on treating colorectal cancer. *Front Immunol*. 2022; 13: 874922.
139. Xu H, Wang Y, Liu G, Zhu Z, Shahbazi MA, Reis RL, et al. Nano-armed limosilactobacillus reuteri for enhanced photo-immunotherapy and microbiota tryptophan metabolism against colorectal cancer. *Adv Sci (Weinh)*. 2025; 12: e2410011.
140. Li C, Sun YD, Yu GY, Cui JR, Lou Z, Zhang H, et al. Integrated omics of metastatic colorectal cancer. *Cancer Cell*. 2020; 38: 734-47.e9.
141. Tao Y, Xing S, Zuo S, Bao P, Jin Y, Li Y, et al. Cell-free multi-omics analysis reveals potential biomarkers in gastrointestinal cancer patients' blood. *Cell Rep Med*. 2023; 4: 101281.

142. Gerovska D, Larrinaga G, Solano-Iturri JD, Márquez J, García Gallastegi P, Khatib AM, et al. An integrative omics approach reveals involvement of *BRCA1* in hepatic metastatic progression of colorectal cancer. *Cancers (Basel)*. 2020; 12: 2380.
 143. Shi M, Yang Y, Huang N, Zeng D, Mo Z, Wang J, et al. Genetic and microenvironmental evolution of colorectal liver metastases under chemotherapy. *Cell Rep Med*. 2024; 5: 101838.
 144. Zou J, Zhang H, Huang Y, Xu W, Huang Y, Zuo S, et al. Multi-omics analysis of the tumor microenvironment in liver metastasis of colorectal cancer identified FJX1 as a novel biomarker. *Front Genet*. 2022; 13: 960954.
 145. Wong GYM, Li J, McKay M, Castaneda M, Bhimani N, Diakos C, et al. Proteogenomic characterization of early intrahepatic recurrence after curative-intent treatment of colorectal liver metastases. *J Proteome Res*. 2024; 23: 4523-37.
- Cite this article as:** Zhou K, Yang C, Li Y. Multi-omics in colorectal cancer liver metastasis: applications and research advances. *Cancer Biol Med*. 2025; 22: 618-638. doi: 10.20892/j.issn.2095-3941.2025.0066