

# Emerging Mechanisms and Treatment Progress on Liver Metastasis of Colorectal Cancer

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**Abstract:** Colorectal cancer is currently the third largest malignant tumor in the world, with high new cases and high mortality. Metastasis is one of the most common causes of death of colorectal cancer, of which liver metastasis is the most fatal. Since the beginning of the Human Genome Project in 2001, people have gradually recognized the 3 billion base pairs that make up the human genome, of which only about 1.5% of the nucleic acid sequences are used for protein coding, including proto-oncogenes and tumor suppressor genes. A large number of differences in the expression of proto-oncogenes and tumor suppressor genes have also been found in the study of colorectal cancer, which proves that they are also actively involved in the progression of colorectal cancer and promote the occurrence of liver metastasis. Except for 1.5% of the coding sequence, the rest of the nucleic acid sequence does not encode any protein, which is called non-coding RNA. With the deepening of research, genome sequences without protein coding potential that were originally considered “junk sequences” may have important biological functions. Many years of studies have found that a large number of abnormal expression of ncRNA in colorectal cancer liver metastasis, indicating that ncRNA plays an important role in it. To explore the role and mechanism of these coding sequences and non-coding RNA in liver metastasis of colorectal cancer is very important for the early diagnosis and treatment of liver metastasis of colorectal cancer. This article reviews the coding genes and ncRNA that have been found in the study of liver metastasis of colorectal cancer in recent years, as well as the mechanisms that have been identified or are still under study, as well as the clinical treatment of liver metastasis of colorectal cancer.

**Keywords:** colorectal cancer, liver metastasis, mechanisms, treatment

## Introduction

Colorectal cancer has about 1.4 million new cases and 694,000 deaths worldwide every year, making it the third largest malignant tumor in the world.<sup>1,2</sup> Metastasis is the most common cause of death from colorectal cancer, while liver metastasis is the most common.<sup>3-5</sup> Some studies have shown that liver metastasis accounts for 75–83% of colorectal cancer metastasis.<sup>6,7</sup> Therefore, the early diagnosis of liver metastasis of colorectal cancer is very important to reduce the mortality of patients. Due to the lack of sensitivity and specificity of serum markers such as CEA, in the diagnosis of colorectal cancer liver metastasis, the diagnosis of colorectal cancer liver metastasis still depends on imaging examination and focus biopsy.<sup>8-10</sup> However, the sensitivity of imaging diagnosis of liver metastasis of colorectal cancer is still insufficient to achieve the effect of early diagnosis, so it is imperative to find a new biomarker that can better diagnose liver metastasis of colorectal cancer.

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The mechanism of liver metastasis of colorectal cancer has not been fully elucidated. Current studies have shown that tumor cells spread from primary to distant organs and develop into metastatic foci, which is a continuous dynamic process with the participation of multiple genes and multiple links. It involves many links, such as tumor cell adhesion, invasion, extracellular matrix remodeling, neovascularization and lymphangiogenesis, body immunity and so on.<sup>11</sup> In recent years, the relationship between abnormal expression of tumor genes and liver metastasis of colorectal cancer has become the focus of tumor molecular biology research, and made a breakthrough. Liver metastasis of colorectal cancer must have two prerequisites: first, colon cancer cells themselves have high metastatic characteristics; second, there must be target organs suitable for the growth of metastatic colon cancer cells. Thus, it can be seen that a large number of mutations of oncogenes or tumor suppressor genes make colon cancer cells easy to metastasize, and the liver is an organ suitable for the growth of metastatic colon cancer cells, both of which promote liver metastasis of colorectal cancer and lead to poor prognosis.

Over the past 10 years, with the development of next generation sequencing and bioinformatics, there has been a great variety. Thousands of Non-coding RNA has been discovered. In a sense, only the open reading frame (ORF) sequence on mRNA is the “coding” sequence, while other sequences on mRNA and a large number of non-mRNA transcripts that can not be used as translation templates are called non-coding RNA sequences.<sup>12–14</sup> The non-coding RNA sequence on mRNA can regulate the translation, location and stability of mRNA.<sup>15–20</sup> More and more evidence shows that ncRNA plays an important role in the occurrence, development and metastasis of colorectal cancer. It can be used not only as a tumor suppressor, but also as an oncogene to regulate the expression of its specific mRNA target.<sup>21–26</sup>

In this review, we summarize the research progress of coding genes and non-coding RNAs in colorectal liver metastasis, and briefly introduce the progress in clinical treatment in recent years. It is expected to contribute to the early detection and early treatment of liver metastasis of colorectal cancer, and to prolong the survival time and quality of life of patients.

## Brief Overview of Coding Genes

Malignant tumor causes serious harm to human health, and its occurrence is the result of the joint action of multi-

factors, multi-stages and multi-genes, which is closely related to the disturbance of cell cycle and apoptosis regulation. In the occurrence and development of tumor, when various environmental factors and genetic pathogenic factors cause DNA damage, thus activating proto-oncogenes and inactivating tumor suppressor genes, resulting in disturbance of cell cycle regulation and imbalance of apoptosis regulation, resulting in abnormal cell growth, is the most fundamental cause of tumorigenesis. We sorted out the coding genes and their products that have been found in the research of colorectal cancer liver metastasis (CRLM) in recent years, and briefly worked out the mechanism in Table 1.

## The Role of Tumor Suppressor Genes in Liver Metastasis of Colorectal Cancer

Tumor suppressor genes are a kind of genes that exist in normal cells which can inhibit cell growth and have potential anti-tumor effect. Tumor suppressor genes play a very important negative regulatory role in controlling cell growth, proliferation and differentiation. They restrict each other with proto-oncogenes and maintain the relative stability of positive and negative regulatory signals. When these genes are mutated, deleted or inactivated, they can cause malignant transformation of cells and lead to tumorigenesis. So far, scientists have isolated and identified about 100 kinds of tumor suppressor genes from cells, the most common of which are Rb, p53, APC, nm23 and so on. According to whether there is a mutation, it can be divided into two types: mutant type and wild type, and according to different acting organs, it can be divided into broad spectrum and specificity. Different tumor suppressor genes have different functions. Some of them can participate in cell signal transduction and epigenetic regulation, some can negatively regulate cell cycle, some can lead to DNA mismatch repair, some can regulate development and stem cell proliferation, and some can be used as negative transcriptional factors. These functions can participate in the occurrence and development of tumor. In CRLM, some tumor suppressor genes are also involved and play an irreplaceable role. The abnormally expressed tumor suppressor genes found in CRLM in recent years were sorted out in Table 1.

### PTEN

PTEN gene (phosphatase and tensin homologue deleted on chromosome 10), also known as advanced tumor mutant gene, is the first tumor suppressor gene with dual specific

**Table I** Coding Genes in Liver Metastasis of Colorectal Cancer

Genes	Major Effects	Receptors/ Inhibitor	Reference
CXCL8	CXCL8 and its receptors have also been known to induce the epithelial-mesenchymal transition (EMT) of CRC cells, to help them to escape host immunosurveillance as well as to enhance resistance to anoikis, which promotes the formation of circulating tumor cells (CTCs) and their colonization of distant organs.	CXCR1, CXCR2, DARC	[60]
HMGA2	By forming a circNSUN2/IGF2BP2/HMGA2 RNA-protein ternary complex in the cytoplasm, circNSUN2 enhances the stability of HMGA2 mRNA to promote CRC metastasis progression.	circNSUN2	[108]
GATA6	Via GATA6, metastatic cells in the liver upregulate the enzyme aldolase B (ALDOB), which enhances fructose metabolism and provides fuel for major pathways of central carbon metabolism during tumor cell proliferation.	ALDOB	[124]
CXCR4	CXCR4/TGF- $\beta$ 1 axis plays an important role in CRC liver metastasis through mediating HSCs differentiation into CAFs.	TGF- $\beta$ 1	[59]
DC-SIGNR	DC-SIGNR conferred metastatic capability on cancer cells by upregulating various metallothionein isoforms.	–	[125]
IGFBP7	IGFBP7 may prevent colon cancer metastasis by inhibiting EMT.	–	[126]
PRRX2	PRRX2 inhibition may reduce invasive and migrating abilities to hinder epithelial-mesenchymal transition (EMT), and suppress colon cancer liver metastasis through inactivation of Wnt/ $\beta$ -catenin pathway.	Wnt/ $\beta$ -catenin signaling pathway	[127]
KRAS	Amplification of ERK1/2 signaling in KRAS-mutated colorectal cancer cells affects the cytokine milieu of the tumors, possibly affecting tumor-stroma interactions and favoring liver metastasis formation.	ERK1/2 signaling	[128]
PTGIS	PTGIS expression and lymph node metastasis are independent risk factors for liver metastasis of colon cancer.	–	[129]
Gli-1	Gli-1 is significantly up-regulated in colon cancer, which may be closely related to liver metastasis. The mechanism is not clear.	–	[130]
Wtp53	Wtp53 has synergistic effect with TK/GCV and CD/5-FC, which can effectively inhibit the formation of liver metastasis of colon cancer.	–	[33]
CXCL1	TSU68 can significantly reduce the expression of CXCL1 in colon cancer with liver metastasis.	TSU68	[131]
VEGF TIMP-1	The high levels of VEGF and TIMP-1 were found to be significant predictive factors for poor prognosis following liver resection.	–	[132–135]
SDF-1	Arrest of CXCR4 can inhibit liver metastasis of colon cancer through blocking cell proliferation and migration induced by SDF-1.	CXCR4	[136]
Galectin-3	The expression of galectin-3 is significantly increased in the liver metastasis of colon cancer.	–	[137]
TROP2	TROP2 is highly expressed in liver metastatic cells of colorectal cancer and significantly reduces the survival time.	–	[138]
NK4	Hepatic gene expression of NK4 inhibited the liver metastasis and subsequent growth associated with a decrease in microvessel density.	–	[139]
TFF3	TFF3 is highly expressed in liver metastasis of human colon cancer and increases the ability of invasion and metastasis.	–	[140]

(Continued)

Table 1 (Continued).

Genes	Major Effects	Receptors/ Inhibitor	Reference
TIMP-1	High expression of TIMP-1 can effectively combat MMPs, in tumor tissue and inhibit liver metastasis of colon cancer.	MMPs	[141]
FAS	FAS is highly expressed in liver metastatic tumor cells of colon cancer.	–	[142]
SLeX	Cancer cells expressing SLeX can adhere to hepatic sinusoidal endothelial cells treated with IL-1 $\beta$ through SLeX- selectin interaction system, which may be the first step in the metastasis of colon cancer cells to liver.	IL-1 $\beta$	[143]
PRDX4	High expression of PRDX4, CKS2, MAGED2 and EST in Colorectal Cancer with liver Metastasis	–	[144]
CKS2			
MAGED2			
EST			
CCR1	Lack of the CCR1, MMP2, MMP9 gene in the host dramatically suppresses outgrowths of disseminated colon cancer in the liver	CCL9, CCL15	[145–147]
MMP2			
MMP9			
PA	PALS can inhibit the expression of PA and has an inhibitory effect on colorectal liver metastasis	PALS	[148]
TGF- $\beta$	Promote tumor growth, invasion and metastasis in in liver metastasis of colon cancer	LY2109761	[149]
STRAIL	STRAIL and actinomycin D can synergistically inhibit multiple intrahepatic metastasis of TRAIL-resistant colon cancer	–	[150]
EMX2	The decreased expression of EMX2 promotes distant liver metastasis and reduces the survival rate of colorectal cancer, but the exact mechanism is still unknown	–	[151]
THBS-1	Low expression of THBS-1 promotes liver Metastasis of Colorectal tumor and EMT, may be regulated by HIF-1 Pathway	HIF-1	[152]
Integrin $\beta$ 4	ZKSCAN3 can promote the expression of integrin $\beta$ 4 and VEGF, which may promote the liver metastasis of CEA related colorectal cancer, especially in the cases of CEA tumor.	ZKSCAN3	[153]
VEGF			
SNCG	High expression of SNCG is present in the tumor tissue in patients with liver metastasis from colorectal cancer. The mechanism is not clear.	–	[54]
TBLIXR1	For stage IV CRC patients, TBLIXR1 expression was correlated with the number of liver metastases, and high levels of TBLIXR1 in liver metastases indicated poor overall survival.	–	[154]
Smad4	Knockdown of Smad4 ERK pathway, altered the expression of MMP2 and COX-2, promoted cell motility, migration, and invasion in vitro, enhanced metastasis.	ERK pathway	[155]
Fbxw7	Fbxw7 expression in tumor tissues was significantly lower than that in normal tissues, miR-223 might be a possible regulator of Fbxw7.	miR-223	[156]
APOBEC3G	APOBEC3G promotes colorectal cancer hepatic metastasis through inhibition of miR-29-mediated suppression of MMP2.	miR-29 MMP2	[157]
AEG-1	The expression of AEG-1 protein was significantly increased in tumor cells with liver metastasis.	–	[158]
DVLI	DVLI is significantly overexpressed in CRC patients with liver metastasis.	–	[159]

(Continued)

Table I (Continued).

Genes	Major Effects	Receptors/ Inhibitor	Reference
Claudin1	Claudin1 and claudin4 gene knockout can significantly promote tumor cell migration and inhibit clonal growth, and reduce the overall survival rate.	–	[160]
Claudin4			
USP22	The expression level of USP22 in primary cancer tissue and liver metastatic carcinoma was significantly increased.	–	[161]
MACC1	MACC1 expression level might play an important role in colon cancer invasion.	–	[162]
SI00B	The expression of SI00B and TM4SF4, OLFM4 genes in liver metastatic tumor cells of colon cancer was significantly up-regulated.	–	[163]
TM4SF4			
OLFM4			
CCL7	The expression of CCL7 genes in liver metastatic tumor cells of colon cancer was significantly up-regulated.	–	[164]
PSMA7	The expression of PSMA7 in liver metastases is significantly higher than that in primary lesions and lymph nodes, suggesting that PSMA7 may play an important role in the development of colorectal cancer.	–	[165]
HGF	HGF is highly expressed in colorectal cancer with liver metastasis. HGF-c-Met may play a role in colorectal cancer with regional lymph node metastasis.	c-Met	[166]
SI00A6	SI00A6 is involved in the invasion of colorectal adenocarcinoma and its expression level decreases in liver metastases.	–	[167]
PRL-3	PRL-3 and c-myc genomic gain may represent an aggressive phenotype of primary CRC, and may associate with liver metastasis.	–	[168,169]
c-myc			
CRPSNP rs7553007	The mutation rates of CRPSNP rs7553007 and KRAS/BRAF genes were significantly increased in patients with colorectal cancer complicated with liver metastasis, and cooperated with C-reactive protein to promote liver metastasis.	–	[170]
BRAF			
ZFP57	The expression of ZFP57 in tumor cells with liver metastasis was significantly higher than that in tumor cells without liver metastasis, and the overexpression of ZFP57 decreased the progression-free survival rate.	–	[171]
PIK3CA	Colon cancer patients with PIK3CA and PTEN gene mutations have a significantly higher rate of liver metastasis and a poor prognosis.	–	[172]
PTEN			
Ereg	Ereg, AREG, COX-2, LCK are closely related to liver metastasis of colorectal cancer and can be used to predict liver metastasis of colorectal cancer.	–	[173]
AREG			
COX-2			
LCK			
DYRK2	In the model of xenotransplantation in vivo, the ectopic expression of DYRK2 significantly reduced the focus of liver metastasis, and the overall and disease-free survival rate of patients with liver metastasis with low expression of DYRK2 was significantly poor.	–	[174]
SIPRI	The up-regulation of SIPRI expression is closely related to the deep invasion and metachronous liver metastasis.	–	[175]

(Continued)

Table 1 (Continued).

Genes	Major Effects	Receptors/ Inhibitor	Reference
CXCL16	Chemokine CXCL16 suppresses liver metastasis of colorectal cancer via augmentation of tumor-infiltrating natural killer T cells.	NKT cells	[176]
HNF4 $\alpha$	The expression of HNF4 $\alpha$ was significantly down-regulated in many kinds of tumor cells and in liver metastatic cells of colon cancer, suggesting that HNF4 $\alpha$ has the effect of inhibiting liver metastasis.	–	[177]
IGF-IR	Mutant KRAS transcriptionally activates IGF-IR gene expression through Y-box-binding protein (YB)-1 upregulation via a novel MEK-Sp1-DNMT1-miR-137 pathway in CRC cells.	KRAS	[178,179]
CDX2	CDX2 participates in the expression of DNA repair protein through Wnt signal transduction and leads to methylation. The loss of CDX2 expression is an important mechanism of liver metastasis in colorectal cancer.	Wnt signal transduction	[180]

phosphatase activity cloned from primary breast cancer, prostate cancer and glioblastoma cell lines in 1997.<sup>27</sup> The anti-tumor effect of PTEN is mainly through MAPK pathway, PI3K/Akt pathway, FAK pathway and cell cycle pathway to participate in normal cell development and inhibit angiogenesis. The subcellular localization of PTEN is very important for its normal cellular function and its role as a tumor suppressor. In colorectal cancer, the mutation rate of PTEN gene is 6%, indicating that PTEN also has a high mutation rate in CRLM. In the cytoplasm, PTEN binds with its cytoplasmic targets to regulate cell proliferation, apoptosis, cell cycle progression, cell adhesion, migration and invasion. In the nucleus, PTEN plays a role in maintaining chromosome stability and DNA double-strand break repair, thus maintaining the integrity of the genome.<sup>28</sup> The mislocalization of PTEN between nucleus and cytoplasm may lead to malignant growth.<sup>29</sup> Therefore, the subcellular localization of PTEN is closely regulated and a variety of regulatory mechanisms have been found.

PI3K/Akt signaling pathway is an important intracellular signal transduction pathway, which plays an important biological role in cell apoptosis, survival, proliferation and cytoskeleton changes. Its regulation disorder is closely related to the occurrence and development of tumor. Receptor tyrosine kinase (RTK) is the main upstream regulator of PI3K/Akt signal. PTEN is the main antagonist of PI3K and a negative regulator of this pathway. Inactivation of PTEN will lead to excessive activation of RTK/PI3K/Akt signal in many tumor types, thus driving tumorigenesis.<sup>30</sup>

Related studies found that in CRLM, the mutation rate of PTEN gene increased significantly, and suggested that

the prognosis is obviously poor, PTEN gene may also be involved in liver metastasis through the above mechanism, but the related research has not yet been carried out, we can know the next research direction.

### WTp53

P53 gene is a tumor suppressor gene, located on the short arm of chromosome 17p. 20 kb, encodes a tumor suppressor protein Tp53, with a molecular weight of 53 kD, which is involved in the control of a variety of cell events, such as cell cycle regulation, apoptosis, cell senescence, DNA repair, cell differentiation, gene amplification, DNA recombination, chromosome segregation and angiogenesis. P53 gene can be divided into wild type (WTp53) and mutant type (MTp53). The anti-tumor effect of WTp53 mainly prevents cells from entering S phase in G1/G0 phase, which inhibits cell proliferation and induces cell apoptosis.<sup>31</sup> When the p53 gene is mutated, the stable protein can not inhibit the cell proliferation, promote the malignant transformation of the cell, enhance the invasiveness, and make the p53 gene change from tumor suppressor gene to proto-oncogene.

The occurrence of liver metastasis of colorectal cancer is mainly caused by reflux of portal vein and hepatic artery, in which the formation of tumor neovascularization is very important.<sup>32</sup> Du T found that WTp53 has a synergistic effect with TK/GCV and CD/5-FC to inhibit tumor neovascularization and prevent liver metastasis.<sup>33</sup>

### Claudin

In humans and animals, there is a tight junction between adjacent epithelial or endothelial cells. Tight junction is one of the main forms of cell adhesion. It is



a macromolecular complex composed of cytoplasmic proteins and transmembrane proteins. It is the structural and functional basis of paracellular material transport pathways. It mainly has barrier and screening functions, which can maintain the stability of the internal environment of the body and maintain the polarity of epithelial cells. It plays an important role in the normal physiological process of cells. Claudins is a cytoskeleton protein of tight junction between cells and an important component of tight junction molecules. Its abnormal expression can lead to structural damage and functional damage of epithelial cells and endothelial cells, and then lead to tumor invasion and metastasis.

In 1998, in the study of transmembrane protein, Furuse found and identified a complete tight junction fragment in chicken liver for the first time, its relative molecular weight was 22,000, and named it Claudin.<sup>34</sup> So far, 27 members of the Claudins protein family have been found in humans, with a sequence identity of 12.5%–69.7%, most of the relative molecular weight is 20,000–27,000. So far, 21 species have been identified to exist in the human body.<sup>35</sup>

Each molecular structure consists of four transmembrane domains and two extracellular annular domains. In the extracellular annular regions, the larger primary macrocycle is composed of 52 amino acid residues, while the secondary ring is composed of 16,033 residues. The same is that the terminal structures of amino and carboxyl groups are present in the cytoplasm, and there is a specific PDZ binding region on it. Among different Claudins protein molecules, the C-terminal sequence has different lengths of 210.63 residues, and the amino acid sequences of the first and fourth transmembrane fragments and the outer ring are highly conserved. These two annular structures of Claudins protein can contact the outside world through homologous or heterologous ways: (1) the longer extracellular ring mainly forms two different kinds of intercellular pores of paracellular open or closed, and these pores are the important structural basis for the formation of tight junctions, and pores play an important role in the formation of tight junction bands and ion-selective permeability. (1) the longer extracellular rings mainly form two different kinds of intercellular pores, which are open or closed, and these pores play an important role in the formation of tight junction bands and ion selective permeability. (2) the shorter extracellular loop is mainly responsible for the trans-binding between Claudins molecules and does not participate in the regulation of paracellular

permeability, and the shorter extracellular loop is the binding site of enterotoxin from *Cystitis perfringens*, while the intracellular C-terminal is connected to tight junction protein (zonula occludens, ZO) molecules through different PDZ domains.<sup>36</sup>

The expression of Claudins protein is specific, and more than two kinds of Claudins protein molecules can be expressed in most tissues and organs. They are expressed not only in the tight junction but also on the side of some epithelial cells and on the basement membrane. It has been found that there are abnormal expressions of Claudin1 and Claudin4 in CRLM. Claudin1 can promote the activation of matrix metalloproteinase-2 precursor and enhance the ability of invasion and metastasis of cancer cells. At the same time, the increased expression of Claudin1 can inhibit the expression of E-cadherin, Claudin1 may be the target gene of  $\beta$ -catenin/Tcf (T cell factor) signal pathway, the up-regulation of  $\beta$ -catenin/Tcf signal pathway can promote the occurrence and development of tumor, while the decreased expression of E-cadherin can promote the up-regulation of  $\beta$ -catenin/Tcf signal pathway, so the overexpression of Claudin1 can promote tumorigenesis.<sup>37</sup> Claudin4 was previously low or non-expressed in colon cancer cells and highly expressed in cholangiocarcinoma. Recently, it has been found that Claudin4 is highly expressed in CRLM, but the specific mechanism remains to be studied.

## The Role of Oncogenes in Liver Metastasis of Colorectal Cancer

Proto-oncogenes exist in the genomes of normal biological cells. Like tumor suppressor genes, proto-oncogenes play an important role in the regulation of cell growth and proliferation. Under normal circumstances, the ability is that the proto-oncogenes in the genome are in a state of low expression or non-expression, but when they encounter certain conditions, such as viral infection, chemical carcinogens or radiation, the proto-oncogenes will be abnormally activated and converted to oncogenes to induce cell carcinogenesis. In Table 2, we sorted out the abnormally expressed oncogenes found in the study of CRLM in recent years.

### MACC1

Metastasis-associated in colon cancer (MACC1) is closely related to liver metastasis of colorectal cancer.<sup>38</sup> It was discovered and named by Stein using differential display RT-PCR technology in 2009. There is a small amount of

**Table 2** Non-Coding RNAs in Liver Metastasis of Colorectal Cancer

Non-Coding RNAs	Expression	Major Effects	Targets	Reference
NSUN2 (CircRNA)	Up	Enhance the stability of HMGA2 mRNA by forming a circNSUN2/IGF2BP2/HMGA2 RNA-protein ternary complex	HMGA2	[108]
0001178 (CircRNA)	Up	–	–	[181]
CSPP1 (CircRNA)	Up	Competitively binding to miR-193a-5p and preventing miR-193a-5p from decreasing the expression of COL1A1	COL1A1	[182]
0000826 (CircRNA)	Up	–	–	[183]
Circ-133 (CircRNA)	Up	Exosomal circ-133 derived from hypoxic cells delivered into normoxic cells and promoted cancer metastasis by acting on miR-133a/GEF-H1/RhoA axis	GEF-H1 /RhoA	[103]
102049 (CircRNA)	Up	Significantly enhanced the adhesion, migration and invasion abilities of CRC cells, and promoted CRC progression via a miR-761/miR-192-3p-FRAS1-dependent mechanism	FRAS1	[184]
CLMAT3 (lncRNA)	Up	–	–	[185]
UICLM (lncRNA)	Up	Acted as a ceRNA for miR-215 to regulate ZEB2 expression	ZEB2	[92]
HOXA11-AS (lncRNA)	Up	Functioning as a miR-125a-5p sponge, promote the expression of PADI2	PADI2	[101]
SNHG7 (lncRNA)	Up	Functioning as a miR-216B sponge, promote the expression of GALNT1	GALNT1	[186,187]
CRNDE (lncRNA)	Up	–	–	[187]
SNHG15 (lncRNA)	Up	–	–	[188]
RP11-757G1.5 (lncRNA)	Up	RP11-757G1.5 regulated the expression of YAP1 through sponging miR-139-5p	YAP1	[189]
B3GALT5-AS1 (lncRNA)	Down	Directly bound to the promoter of miRNA-203, repressed miR-203 expression, upregulated miR-203 targets ZEB2 and SNAI2, and induced epithelial-to-mesenchymal transition (EMT)	ZEB2, SNAI2	[190]
miR-146a (miRNA)	Up	Impede c-met and NUMB translation	c-met, NUMB	[191,192]
miR-17 (miRNA)	Up	–	–	[193]
miR-487b (miRNA)	Down	miR-487b directly targeted LRP6, a receptor for WNT/β-catenin signaling and suppress metastasis of CRC progression through inhibition of KRAS	LRP6, KRAS	[83]
miR-320a (miRNA)	Down	miR-320a directly binds to the 3'UTR of neuropilin 1 (NRP-1), a protein that functions as a co-receptor of vascular epithelial growth factor	NRP-1	[194]
miR-122 (miRNA)	Up	Concomitant suppression of CAT1 in the primary tumor appears to play important roles in the development of colorectal liver metastasis	CAT1	[195–197]
miR-340 (miRNA)	Down	Inhibite growth of colon cancer cells and suppressed c-Met expression	c-Met	[198]
miR-200b (miRNA)	Down	–	–	[199]
miR-200c (miRNA)				
miR-429 (miRNA)				
miR-126 (miRNA)	Down	–	–	[200]
miR-141 (miRNA)	Up			
miR-21 (miRNA)				
miR-214 (miRNA)	Down	FGFR1 knockdown mimicked the tumor suppressive effect of miR-214 on CRC cells, while reintroduction of FGFR1 abolished the tumor suppressive effect of miR-214 on CRC cells	FGFR1	[201–203]

(Continued)



Table 2 (Continued).

Non-Coding RNAs	Expression	Major Effects	Targets	Reference
miR-574-5p (miRNA)	Up	Played a suppressive role in colorectal cancer liver metastasis by negatively directing MACC-1 expression	MACC-1	[204]
miR-181a (miRNA)	Up	miR-181a has strong tumor-promoting effects through inhibiting the expression of WIF-1, and its potential role in promoting epithelial-mesenchymal transition	WIF-1	[205]
miR-99b-5p (miRNA)	Up	miR-99b-5p silencing in miR-99b-5p-positive CRC cell lines promoted cell migration and up-regulated mTOR	mTOR	[206]
miR-138 (miRNA)	Down	Downregulation of miR-138 as a Contributing Mechanism to Lcn-2 Overexpression in Colorectal Cancer with Liver Metastasis	Lcn-2	[207]
miR-10b (miRNA)	Up	–	–	[208]
miR-203 (miRNA)	Up	–	–	[209]
miR-198 (miRNA)	Down	Tenascin C as a predicted target of miR-198 that promote liver metastasis	Tenascin C	[210]
miR-125a-5p (miRNA)	Down	Participate in liver Metastasis of Colorectal Cancer through miR-125a-5p-PADI2 Regulatory Network	PADI2	[101]
miR-200s (miRNA)	Up	PKC $\zeta$ /ADAR2 axis is a critical regulator of CRC metastases through modulation of miR-200 levels	PKC $\zeta$ / ADAR2	[82]
miR-20a (miRNA)	Up	–	–	[211]
miR-576-5p (miRNA)				
miR-143-3p (miRNA)	Down	–	–	[212]
miR-10b-5p (miRNA)				
miR-21-5p (miRNA)				
miR-518f-5p (miRNA)				
miR-122-5p (miRNA)	Up	–	–	
miR-885-5p (miRNA)				
miR-210-3p (miRNA)				
miR-130b-5p (miRNA)				
miR-1275 (miRNA)				
miR-139-3p (miRNA)				
miR-1290 (miRNA)				
miR-132 (miRNA)	Down	–	–	[213]
miR-378f (miRNA)				
miR-605 (miRNA)				
miR-1976 (miRNA)				
miR-25-3p (miRNA)	Up	M2 polarized macrophages promoted cancer metastasis by enhancing epithelial-mesenchymal transition and secreting vascular endothelial growth factor (VEGF)	VEGF	[214]
miR-130b-3p (miRNA)				
miR-425-5p (miRNA)				

(Continued)

**Table 2** (Continued).

Non-Coding RNAs	Expression	Major Effects	Targets	Reference
miR-139-5p (miRNA)	Down	LncRNA RPI1-757G1.5 regulated the expression of YAPI through sponging miR-139-5p and inhibiting its activity thereby promoting CRC progression and development	YAPI	[189,212]
miR-493 (miRNA)	Down	Inhibit the expression of MKK7 by targeting the 3-UTR binding site of MKK7 gene and promotes liver metastasis of colon cancer cells	IGF1R MKK7	[215]
miR-192 (miRNA)	Down	Downregulate expression of Bcl-2, Zeb2 and VEGFA in vitro and in vivo, which is responsible for enhanced apoptosis, increased expression of E-cadherin and decreased angiogenesis in vivo	Bcl-2, Zeb2, VEGFA	[216]
miR-934 (miRNA)	Up	Induce the polarization of M2 macrophages by down-regulating the expression of PTEN and activating PI3K/AKT signaling pathway, and induces the formation of pre-metastatic niche and promotes the formation of CRLM by secreting CXCL13	PTEN	[217]
miR-215-5p (miRNA)	Down	Low expression of miR-215-5p can reverse the overexpression of CTNNBIP1 and promote distant metastasis.	CTNNBIP1	[218]

MACC1 expression in normal tissues and abnormally high expression in many kinds of malignant tumors, but the expression level is the highest in colon cancer cells. Studies have also shown that the increase of MACC1 expression is often accompanied by the occurrence of malignant tumors, and the 5-year survival rate of patients with high expression of MACC1 mRNA is significantly lower, and the risk of death is increased.<sup>39</sup> MACC1 has a strong correlation with the clinicopathological features, development and prognosis of the tumor, and can be used as an independent evaluation index of metastasis and prognosis.

The MACC1 gene is located on human chromosome 7 (7p21.1), there are about 76,762 base pairs, including 7 exons and 6 introns. Its cDNA has a sequence of 2559 nucleotides and encodes a protein of 852 amino acids. MACC1 protein is a protein complex composed of multiple domains, including ZU5, SH3 and two C-terminal death domains (death domain, DD). It has been found that transfection of MACC1 containing SH3 domain and proline-rich sequence into colon cancer cell lines that do not express MACC1 can enhance cell viability and proliferation, while MACC1 mutants without this domain lack these abilities, indicating that SH3 domain and SH3 binding motif are essential to maintain the biological function of MACC1.

HGF is a multiple growth factor, which is a growth stimulating factor secreted by hepatocytes and endothelial cells.<sup>40</sup> MET protein is encoded by proto-oncogene c-met and is the membrane-specific receptor of HGF.<sup>41</sup> HGF can

bind to specific MET receptors through autocrine, paracrine and classical axonal reverse transport. The combination of the two can activate HGF/MET signal pathway, cause cell proliferation, mucosal epithelial transformation, promote angiogenesis, enhance cell movement, enhance tumor cell invasion and metastasis and so on.<sup>42</sup> MACC1 is a key gene regulating HGF/MET pathway. It has been found that the expression of MACC1 mRNA and MET RNA is high or low in gastrointestinal tumors. As a transcription factor, MACC1 can bind to MET promoter and enhance the expression of MET.<sup>43</sup> MACC1 siRNA can inhibit cell proliferation and movement, reduce metastasis in vivo, and greatly reduce the expression of MET RNA and its protein.

It has been found that the abnormal expression of MACC1 gene plays an important role in CRLM. Stein U experiments have confirmed that MACC1 has the ability to induce cell migration, infiltration and proliferation. They found similar results in vitro and in vivo animal experiments on SW480 cell line from primary focus of colon cancer and liver metastatic cell line SW620 from the same specimen. All these fully show that MACC1 has important research significance in colorectal liver metastasis. It can not only be used as a marker for early diagnosis but also guide clinical treatment and even drug research and development.

## SNCG

$\gamma$ -synaptophysin (SNCG) is a member of the neuronuclear protein family, which is located on chromosome 10q23.2-q23.3. The transcriptional product mRNA is about

100bp, long and encodes a protein of less than 123 amino acid.<sup>44</sup> Ji isolated human breast cancer cDNA library by differential cDNA sequence in 1997.<sup>45</sup> Because of its high expression in advanced breast cancer, it was once called breast cancer-specific gene (BCSGI). However, recent studies have shown that SNCG is highly expressed in many organ tumors, especially in advanced malignant tumors, including breast cancer, ovarian cancer, pancreatic cancer, colorectal cancer and so on. It is almost undetectable or low expression in adjacent non-tumor tissues and is related to tumor invasion and metastasis.

Synaptophysin is a small molecular soluble protein family mainly expressed in nerve tissue, which is distributed among different species and genera, and contains 127–140 amino acid homologous sequences that are highly conserved in the process of evolution. SNCG is located on chromosome 10q23 and is about 5kb in length. It consists of five exons and is transcribed into a mRNA, polypeptide encoding 127AA of 1kb. The results of the SNCG sequence obtained from BAC clone 174P13 and the reported expression sequence tag (expressed sequence tags, ESTs) showed that there were four single nucleotide polymorphism (SNP) sites in the SNCG gene: the upstream-19 site of AUG, the 3 'untranslated region of AUG, the 122bp behind the stop codon UAG, and the third base of the 65th codon. In particular, the change of GTG glutamate GAG in exon 4 leads to the change of amino acid: valine (Val) 110 glutamate (Glu).

A great deal of evidence shows that the abnormal expression of SNCG protein in tumor cells is not due to gene mutation and amplification, but to the activation of transcription.<sup>46,47</sup> There are four main factors that affect the transcription and expression of SNCG: (1) Activator protein 1 (AP1) can activate the AP1 site in the AP1,TPA binding intron through AP1 activators such as TPA to up-regulate the activity of the promoter and increase the expression of SNCG mRNA.<sup>48–50</sup> (2) BubR1 is the main component of the cell division checkpoint, which can monitor the correct assembly of mitotic spindles, so as to ensure the correct separation of homologous chromosomes and prevent cells from escaping the checkpoint to make homologous chromosomes nonsynaptic. SNCG can inhibit the effect of BubR1 by binding to BubR1-microtubulin E (CENP-E) complex, which makes cells escape the control of mitotic checkpoints and form aneuploidy of chromosomes, thus increasing genetic instability and inducing tumorigenesis.<sup>51</sup> (3) CpG island demethylation of SNCG can activate SNCG expression, which is to some extent

consistent with the activation and expression mechanism of proto-oncogenes and growth-related factors in tissue cells.<sup>52</sup> (4) SNCG can promote cell proliferation and inhibit the control of mitotic checkpoints by activating estrogen receptors, leading to tumorigenesis and progression.<sup>53</sup>

The latest study has found that there is a significant high expression of SNCG in CRLM.<sup>54</sup> The 5-year survival rate and prognosis of patients with colorectal liver metastasis with SNCG positive are significantly lower than those with SNCG negative, indicating that the expression of SNCG can be used as an independent prognostic factor for colorectal cancer liver metastasis and can be used as an index for early diagnosis or to guide the next step of treatment.

### Chemokine and Its Receptor

Chemokines are the largest known superfamily of cytokines, and more than 50 kinds of chemokine and more than 20 kinds of chemokine receptors have been found so far.<sup>55</sup> By binding to receptors, chemokines participate in neovascularization,<sup>56</sup> further affect tumor formation and metastasis,<sup>57</sup> and play an important role in liver metastasis of colorectal cancer.

Chemokine is a small molecular cytokine with molecular weight of 8000–12,000, which has chemotactic effect on many kinds of cells, such as neutrophils, lymphocytes, monocytes and so on. According to the position of the conserved sequence of terminal hemistemic acid, they can be divided into four categories: CXC, CC, and CX3C. Chemokines play a role by binding to the corresponding G-protein-coupled receptor superfamily. Chemokines affect tumor in many ways: some chemokines can inhibit tumor growth and development by activating immunoreactive cells or inhibiting tumor-related angiogenesis; other chemokines promote tumor development by enhancing tumor cell proliferation and migration, proteolytic enzyme secretion and inducing tumor angiogenesis, which show that chemokine network involved in tumor formation and metastasis is complex.<sup>58</sup>

There are four steps for cells to overcome vascular endothelial cell barrier between body fluid and tissue: cells flow with body fluid, cells are firmly attached to vascular endothelium, cells pass through endothelial intercellular space, and cells migrate to specific tissues. In this process, chemokines control the selection of exudative cells and the stable adhesion of the selected cells. The migration, invasion and metastasis of tumor cells are affected by chemokines and their receptors. It has been

confirmed that chemokines regulate the metastasis of tumor cells and determine the target tissue of tumor metastasis. The interaction between chemokines specifically expressed in the target organs of tumor metastasis and the corresponding receptors expressed by the tumor can cause the polymerization of intracellular actin and regulate the movement and migration of cells. Therefore, the specific metastasis of tumor cells is closely related to the chemokine receptors expressed by tumor cells and the chemokines expressed by target organs.

There are also many chemokines involved in CRLM. There are also many chemokines involved in CRLM. CXCR4 is a chemokine receptor that plays an important role in CRLM and has a significantly high expression in CRLM, indicating that mediating tumor metastasis can become an important marker for the diagnosis of liver metastasis. The basic steps of the effect of CXCR4 on cancer cell metastasis may be: (1) cloning and expansion of cancer cells, infiltration of local tissue, angiogenesis, and expression of CXCR4; on the surface of tumor cells. (2) the cancer cells fall off from the primary tumor, pass through the lymphatic and vascular walls in the tumor, and enter the systemic circulation. (3) CXCR4 can make cancer cells invade normal tissue through CXCR4/TGF- $\beta$  1 axis, cell expansion and angiogenesis, which leads to liver metastasis.<sup>59</sup> CXCL8 and its receptor CXCR1, CXCR2 can induce epithelial-mesenchymal transformation (EMT), of colorectal cancer cells to help them escape from host immune surveillance and enhance their resistance to aneuploid apoptosis, thus promoting the formation of circulating tumor cells (CTCs) and their colonization in distant organs.<sup>60</sup>

With the further research, it has been found that chemokines and their receptors play a role in promoting distant metastasis in CRLM, but the mechanisms of a small number of chemokines have been declassified, but the mechanisms of most of the chemokines that have been found in CRLM cells are still unclear, which need to be further explored and expected to be transformed into early diagnostic indicators or drugs.

## Brief Overview of Non-Coding RNAs

Over the past 10 years, with the development of next generation sequencing and bioinformatics, there has been a great variety. Thousands of Non-coding RNA has been discovered.<sup>19,20</sup> MiRNA<sup>61–63</sup> and piRNA<sup>64,65</sup> were first

discovered as a kind of small RNA. Then it was discovered that lncRNA. With the increase of species evolution, the number of small RNAs (especially miRNA) and lncRNA gradually increased. In recent years, it has been found that there are a large number of non-coding RNA, namely circRNA, in eukaryotic multicellular organisms.<sup>66–68</sup> With the in-depth study of ncRNA, it has been found that ncRNA can participate in the occurrence and development of tumors through a variety of mechanisms. We summarized the role of ncRNA in liver metastasis of colorectal cancer. In Table 2, we summarize the progress in the field of non-coding RNAs research in recent years.

## The Role of miRNAs in Liver Metastasis of Colorectal Cancer

MiRNA is a class of highly conserved, 18–25 nucleotides long endogenous single-stranded non-coding small molecule RNA.<sup>69</sup> MiRNA exists widely in eukaryotes, and it does not have an open reading frame and does not encode proteins, but miRNA has the characteristics of clustering and can be co-expressed with related genes.<sup>70</sup> In tumors, miRNA usually plays the role of tumor genes or tumor suppressor genes in the occurrence and development of tumors.<sup>71</sup> Onco-miRNA such as miR-21 and miR-10b have oncogene-like functions and are positively correlated with tumorigenesis. Their over-expression or continuous activation will directly lead to tumorigenesis and development.<sup>72,73</sup> Suppressor-miRNA such as miR-15/16 and Let-7 have the function similar to tumor suppressor gene. It has a negative correlation with tumorigenesis, and its down-regulation or inactivation will directly lead to tumorigenesis and development.<sup>74,75</sup>

MiRNA participates in tumorigenesis, development and metastasis in many ways. Drosha and Dicer are members of the RNase III family, mediating the splicing of the double-stranded complex from pri-miRNA to pre-miRNA and from pre-miRNA to miRNA, respectively. Many studies have shown that the expression and activity of Drosha and Dicer participate in the occurrence and development of tumor by affecting the synthesis of mature miRNA.<sup>76,77</sup> Some scholars have proposed the “ceRNA hypothesis”, that is, ceRNA (competing endogenous RNA) can compete with the MRE elements of the 3'-UTR region of tumor genes, tumor suppressor genes and tumor-related signaling pathways to combine with miRNA, antagonize or regulate the function of tumor suppressor or tumorigenic miRNA, so it plays an important role in tumorigenesis, development, invasion, metastasis and drug efficacy.<sup>78</sup>

## The Main Mechanism of miRNAs Regulation in CRLM

In the cells of colorectal cancer liver metastasis (CRLM), researchers found a variety of abnormal expression of miRNA, indicating that miRNA is closely related to colorectal liver metastasis. Among them, epithelial-mesenchymal transition (EMT) is the main mechanism, and most miRNA can directly or indirectly affect EMT to promote the occurrence of liver metastasis. EMT specifically refers to the transformation of cell phenotypes between epithelium and mesenchyme, which was first discovered in the process of embryonic development. In recent years, researchers have gradually paid more and more attention to its role in tumorigenesis and other diseases.<sup>79,80</sup> EMT makes epithelial cells remove differentiated phenotypes, including cell-cell adhesion, top-bottom polarity, low motor ability, and obtain the phenotypes of some mesenchymal cells, including migration, invasion, anti-apoptosis and so on.<sup>81</sup> MiRNAs can regulate EMT through a variety of gene loci in the process of liver metastasis of colorectal cancer. The miRNA-200 family is the hub for the regulation of EMT found by the latest research, which mainly includes miR-200a, miR-200b, miR-200c, miR-200s, miR-141, miR-429 and so on. The study of Shelton Pm found that the expression of miR-200s was significantly increased in CRLM. It promotes metastasis and regulates EMT through the PKC  $\zeta$ /ADAR2 axis.<sup>82</sup> KRAS is an important targeted tumor suppressor gene. In tumors, the miRNAs, cascade of some targeted oncogenes KRAS activates KRAS, activated RAS response original binding protein (RREB1), which directly inhibits the transcription of miRNA clusters including miR-384, miR-487b and down-regulates the expression of KRAS in subcutaneous or xenotransplanted tumors by transcriptional up-regulation of these miRNA or liposome delivery systems.<sup>83</sup> At the same time, a variety of miRNAs can pass through various signals such as mTOR, PTEN, PKC $\zeta$ /ADAR2, etc, affect the proliferation of blood vessels around the tumor, reduce tumor cell adhesion, and promote the progress of CRLM.

Thus, many miRNAs have been found in CRLM, and the related mechanisms of their regulation of CRLM are gradually becoming clear. It is believed that miRNA will play an important role in the diagnosis and treatment of CRLM.

## The Role of lncRNAs in Liver Metastasis of Colorectal Cancer

In 2002, Japanese researchers first put forward the concept of lncRNA, which refers to non-coding RNA with a length

of more than 200 nt.<sup>84</sup> Until 2007, a highly expressed functional lncRNA gene of 2.2 kb was found for the first time in breast cancer, proving the role of lncRNA in tumorigenesis and development.<sup>85</sup>

lncRNA has a 5'-cap structure and a 3'-terminal polyadenylate tail, and its gene structure is similar to that of mRNA.<sup>86</sup> lncRNA can act as the sponge of microRNA and adsorb some specific microRNA, in the way of bait so as to regulate the expression of some microRNA target genes. The lncRNA with this function is also known as ceRNA (Competing endogenous RNA).<sup>87</sup> At the same time, because the expression of most long non-coding genes is transcribed by RNA polymerase II (RNAP II), the specific expression of these genes in tissues and developmental stages indicates that the transcription of these genes is strictly regulated, so people can infer the state of chromatin according to the expression of lncRNA. In addition, lncRNA can also regulate tumor suppression or oncogene expression. Many studies have shown that lncRNA has a variety of other effect mechanisms, it can be used as signal molecules, bait molecules and guiding, functional scaffolds, but also can interact with other biomolecules to form a certain module structure to exert its biological function.<sup>88,89</sup> It can be seen that lncRNA is closely related to the occurrence and development of tumors.<sup>90</sup>

## The Main Mechanism of lncRNAs Regulation in CRLM

ZEB2 can directly down-regulate the expression of cell junction-related genes, including adhesive junctions, tight junctions, desmosomes and gap junctions. ZWB2 can increase the expression of interstitial proteins (such as vimentin and N-cadherin), which is common in the cell cord of hepatocellular carcinoma.<sup>91</sup> The study of Chen D1 found that the expression of lncRNA-UICLM in CRLM was significantly increased, while the expression of tumor suppressor gene ZEB2 was significantly decreased. Further study of the mechanism found that lncRNA-UICLM is a competitive endogenous RNA, of miR-215, that is, lncRNA-UICLM can be used as a "sponge" of miR-215, that is, it absorbs miR-215, to inhibit the expression of ZEB2 and accelerate the occurrence of liver metastasis of colorectal cancer.<sup>92</sup>

PDI2 (Peptidyl arginine deiminase 2) was first confirmed in animal experiments to have a high expression in HER2/ERBB2 (+) breast cancer, and when PDI2 is inhibited, the tumor cells will be significantly suppressed. Several recent studies have reported that PDI2 is involved in tumorigenesis and plays an important role in the development of many



malignant tumors such as spontaneous skin tumors, multiple myeloma, breast cancer and colorectal cancer.<sup>93–95</sup> MiR-125a-5p is a classic tumor suppressor gene. At present, many studies at home and abroad have found that it can effectively inhibit the invasion and metastasis of common tumors, including hepatocellular carcinoma, gastric cancer, breast cancer, lung cancer, glioma, melanoma and so on. The regulatory targets of its inhibitory effect in different tumors are SIRT7, PI3K, E2F3, ERBB2, TSTA3, HDAC4, HDAC5, EGFR, Gab2, Lin28B and other genes.<sup>96–100</sup> Chen et al found that lncRNA HOXA11-AS can act as a “sponge” of miR-125a-5p, promoting the expression of PADI2, which leads to liver metastasis of colorectal cancer.<sup>101</sup>

LncRNA can affect the occurrence and development of CRLM through a variety of mechanisms, but it is still necessary to further explore the different mechanisms and pathways of different lncRNA, which is very important for the early diagnosis and even treatment of CRLM in the future.

## The Role of circRNAs in Liver Metastasis of Colorectal Cancer

The role and mechanism of circRNA in tumor is one of the recent research hotspots. In 2013, Jeck detected more than 25,000 circRNAs in human fibroblasts.<sup>68</sup> They realized that circRNA is widespread in the human body and may play an important role in the spectrum of human diseases. CircRNA is a special type of endogenous non-coding RNA whose 3' end and 5' end are connected to form a closed covalent ring structure. This structure makes circRNA more stable and highly conserved. Since circRNA has one or more miRNA binding sites, it can reduce the activity of miRNA by binding to miRNA, weaken the inhibitory effect of miRNA on target genes, thereby regulating the expression of related target genes, and ultimately leading to increased production of messenger RNA. The biological effect is strengthened, this is the competitive-binding mechanism, and this effect is called “miRNA sponge”. At the same time, circRNA can combine with specific proteins to form RNA-protein complexes, thereby affecting protein translation and regulating protein functions.

### The Main Mechanism of circRNAs Regulation in CRLM

In CRLM, most of the circRNA found at present acts as the “sponge” of miRNA to play its role. GRF-H1 is a kind of regulatory protein that regulates the activity of Rho GTP by regulating its GDP/GTP exchange. As an important regulator, it plays an important role in the biological process of

mammals, especially in the proliferation and migration of tumor cells.<sup>102</sup> The study of Yang H found that circ-133 can up-regulate the expression of RhoA by competitively binding to miR-133a in colorectal cancer cells; the overexpression of RhoA can reverse the inhibitory effect of circ-133 on the progression of colorectal cancer, indicating that circ-133 can promote the progression of colorectal cancer through the miR-133a/GEF-H1/RhoA axis.<sup>103</sup>

The HMGA2 gene is located in 12q13-15. There are 5 exons in 200 Kb, and each exon is independently encoded by HMGA2 gene.<sup>104</sup> In normal human tissues, HMGA2 encodes a complete protein product with a relative molecular weight of 12,000. The protein is mainly located in the nucleus and belongs to non-histone chromosome protein.<sup>105</sup> Widely expressed in eukaryotes, it does not have the ability of direct transcriptional regulation, but it can bind to the AT enrichment region of the regulated gene DNA through the unique AT hook structure, causing DNA to bend, stretch, ring or unchain, thus changing the structure of chromatin and enhancing its transcriptional activity, also known as structural transcription factors.<sup>106</sup> Transcripts of HMGA2 gene can hardly be detected in normal adult tissues. In recent years, studies have shown that HMGA2 is abnormally expressed in a variety of cancer tissues, and participates in the regulation of a variety of biological behaviors, and plays a role in promoting the occurrence and development of cancer. The degree of expression is closely related to the clinicopathological features and the survival and prognosis of patients.<sup>107</sup> Chen RX's study found that CircNSUN2 and HMGA2 were highly expressed in colorectal liver metastatic cancer cells. Further studies showed that N6-methyladenosine modification of CircNSUN2 increased cytoplasmic output, thus through the formation of CircNSUN2/IGF2BP2/HMGA2RNA-protein ternary complex in the cytoplasm to enhance the stability of HMGA2 mRNA and promote colorectal cancer metastasis.<sup>108</sup>

According to the current research, there are still few studies on CRLM in circRNA, but it has been found that circRNA can affect the liver metastasis of colorectal cancer through different mechanisms. For example, as a sponge of miRNA, or regulating the expression of coding genes, it is proved that circRNA plays an important role in the occurrence of CRLM, which points out the direction for further research.

## Clinical Treatment of Liver Metastasis of Colorectal Cancer

The liver is one of the most common organs with distant metastasis of colorectal cancer. Correct and effective



treatment of liver metastasis can not only delay the progress of the disease and prolong the life span of patients but also provide a good guarantee for the quality of prognosis of patients. At present, surgical resection is still the first choice for liver metastasis of colorectal cancer. With the continuous development of related technologies and the in-depth study of liver metastasis of colorectal cancer, new treatment methods such as radiotherapy, cryotherapy and radiofrequency ablation are also being put into practice. Multidisciplinary comprehensive treatment will provide a new research direction for the clinical treatment of liver metastasis of colorectal cancer.

## Surgical Resection

Surgical resection is the first choice for the treatment of liver metastasis of colorectal cancer at present. Standardized surgical treatment is generally advocated for CRC patients with surgical indications.<sup>109</sup> The progress of medicine is changing with each passing day. With the improvement of surgery and multidisciplinary comprehensive treatment, the concept of resectability of liver metastatic cancer is constantly updated. The latest concept of surgical resection is: (1) all metastatic lesions of the liver can be removed; (2) the residual liver volume after resection is more than 30% of the original volume; and (3) extrahepatic metastatic lesions can be removed. At present, experts agree that as long as the residual liver can be compensated, the scope of resection should be expanded as far as possible, so that 20% of patients have the opportunity to operate.<sup>110</sup>

If the primary focus of colorectal cancer is found to have liver metastasis at the same time, or if liver metastasis occurs within 6 months after radical operation, it is called synchronous liver metastasis; if the primary focus is cured for more than 6 months, the recurrent liver metastasis is called metachronous liver metastasis. For patients with simultaneous liver metastasis, surgeons still have difficulties in the choice of simultaneous resection or staging resection. Simultaneous resection avoids the pain of the second operation and correspondingly reduces the incidence of postoperative complications. The survival benefit of staging resection depends on the biological behavior of the tumor, but the operative complications and mortality are higher, but it can make the occult liver metastasis more obvious and reduce the postoperative recurrence rate of simultaneous resection.<sup>109</sup>

To sum up, surgical resection is still the first choice at present, but the formulation of treatment plan needs to be

based on the actual situation of patients, according to multi-disciplinary comprehensive evaluation, and have a real-time understanding of the status of liver metastasis of patients.

## Radiofrequency Ablation Therapy

Radiofrequency ablation is to make the electrode needle directly contact the metastatic tumor tissue under the guidance of ultrasound, CT and laparoscopy, connect the radio frequency current to the electrode needle, and produce heat through the ion shock produced by the current around the electrode needle, so as to achieve the therapeutic purpose of promoting coagulative necrosis of tumor tissue around the electrode needle.<sup>111</sup> In general, the heat production temperature of the target area of radiofrequency ablation electrode needle can be as high as 100 °C, which can cause irreversible thermal coagulation and necrosis of local tissue proteins, apoptosis and micro-circulatory vascular embolism in surrounding tissues, inhibit the formation of blood vessels around the tumor, and prevent the blood dissemination of tumor cells, which has a definite effect on the treatment of liver metastatic lesions of colorectal cancer.<sup>112,113</sup>

The size of liver metastases, the number of liver metastases and the presence or absence of extrahepatic metastasis in patients with colorectal cancer are significantly related to the prognosis, efficacy and survival rate. Studies have shown that patients with liver metastases less than 3 cm in diameter, less than three and without extrahepatic metastasis can be treated with radiofrequency ablation with good accuracy, high repeatability, greater benefit and good prognosis. Most of the patients with liver metastasis of colorectal cancer who can not be operated are due to the lack of liver reserve and complications. In view of this situation, radiofrequency ablation can be used.

## Chemotherapy

As a patient with unresectable colon cancer with liver metastasis, systemic chemotherapy can effectively prolong the survival time. According to the relevant information, the use of oxaliplatin combined with calcium folinate and fluorouracil has achieved considerable results. Using this kind of chemotherapy and continuing to maintain chemotherapy can increase the mPFS of patients with liver metastasis of colorectal cancer (median progression-free survival). However, this kind of method has severe adverse reactions to its own body, which seriously

damages the life and health of patients. However, due to the frequency of chemotherapy, patients with liver metastasis of colorectal cancer are not as tolerant as they used to be.

## Targeted Therapy

The application of molecular targeted therapy strategy to patients with liver metastasis of colorectal cancer also has a certain effect on the improvement of survival time of patients. At present, the selected molecular targeting drugs are mostly used for epidermal growth factor receptor or vascular endothelial growth factor receptor, and the common drugs are panizumab, bevacizumab, cetuximab and so on. Among them, panizumab and cetuximab are mostly used as epidermal growth factor receptor inhibitors, but after more in-depth studies, it is found that the applicable range of the population is gradually shrinking. In addition, cetuximab can be used as a first-line regimen in patients with liver metastasis of colorectal cancer. The obvious effect is the improvement of PFS and OS as well as the efficiency, but it is worth mentioning that if the opposite is a patient with BRAF gene mutation, the effect is very poor. In addition, when bevacizumab and cetuximab were used in patients with liver metastasis of colorectal cancer, the objective effective rate of bevacizumab and cetuximab was not significant. Therefore, in the selection of the above molecular targeted drugs, it is effective for patients with liver metastasis of colorectal cancer, but for patients to have a clear understanding of KRIS, BRAF gene status.

In the selection of molecular targeting drugs mentioned above, it is effective for patients with liver metastasis of colorectal cancer, but it is necessary to have a clear understanding of KRIS and BRAF gene status in patients. As for vascular endothelial growth factor inhibitor, it has not been found that gene status can affect receptor inhibitors. As a result, bevacizumab, which is led by bevacizumab, has gradually become a more respected treatment.

## Immunotherapy

Tumor microenvironment (TME) is a local growth environment composed of tumor cells, tumor stem cells and surrounding infiltrating mesenchymal cells, immune cells, extracellular matrix, interstitial tissue near tumor cells, microvessels, and cytokines.<sup>114</sup> It can be divided into a microenvironment dominated by immune cells and a non-immune microenvironment dominated by fibroblasts.<sup>115</sup> When the tumor cells break through the

immune defense line, the immune cells play an anti-tumor effect at the beginning of tumor invasion, but they also show the role of assisting tumor immune escape and distant metastasis during tumor progression. Immune cell infiltration can secrete inflammatory mediators, creating an inflammatory environment with a high degree of specificity.<sup>116</sup> A variety of immune cells can mediate immune suppression and promote tumor progression in the tumor microenvironment.

With the continuous study of tumor immune mechanisms, immunotherapy has made major breakthroughs in the treatment of malignant tumors. Immunotherapy drugs have achieved many results in clinical trials, and some immunotherapy drugs have been approved for marketing. For CRLM patients, a variety of immunotherapy options can significantly prolong survival, such as tumor vaccines, immunosuppressive agents, and small molecule therapy.

Tumor vaccine therapy uses tumor antigen genes and antigen peptide vaccines to improve the activity of the immune system, and induces the body to produce humoral immunity and cellular immunity through tumor antigen substances and tumor cells to enhance the ability of anti-cancer. Autologous transplantation of dendritic cells (DC) is a classic method of tumor vaccination. DCs can be modified to present tumor antigens and stimulate the adaptive immune system.<sup>117</sup> DC is a powerful TAA presenting cell with MHC (major histocompatibility complex)-I and MHC-II, which activates T cell immunity, has good safety for the treatment of advanced malignant tumors, and can prolong the survival period of CRLM patients.

Cellular immunotherapy refers to the separation of tumor-infiltrating lymphocytes, natural killer cells and other lymphocytes from tumor tissues and blood, which are transformed, activated, expanded and then re-infused into the body to achieve the killing effect on tumor cells. Cellular immunotherapy includes cytotoxic T cell therapy (CTL), genetically modified T cell receptor therapy (TCR-T), lymphokine activated killer cell therapy (LAK) and other treatment options.<sup>118</sup> A recent study showed that cellular immunotherapy combined with oxaliplatin, fluorouracil, and folic acid combined with chemotherapy can appropriately prolong the overall survival and progression-free survival of patients with metastatic colon cancer.<sup>119</sup> TCR-T is a type of cellular immunotherapy. The treatment process is to chimerize tumor-specific antigen receptors into T cells, and then genetically modify T cells back into the body to stimulate T cells to specifically recognize and kill tumor cells. Katz SC's research confirmed that the

percutaneous hepatic artery injection method can significantly reduce the CEA level in patients with liver metastases.<sup>120</sup>

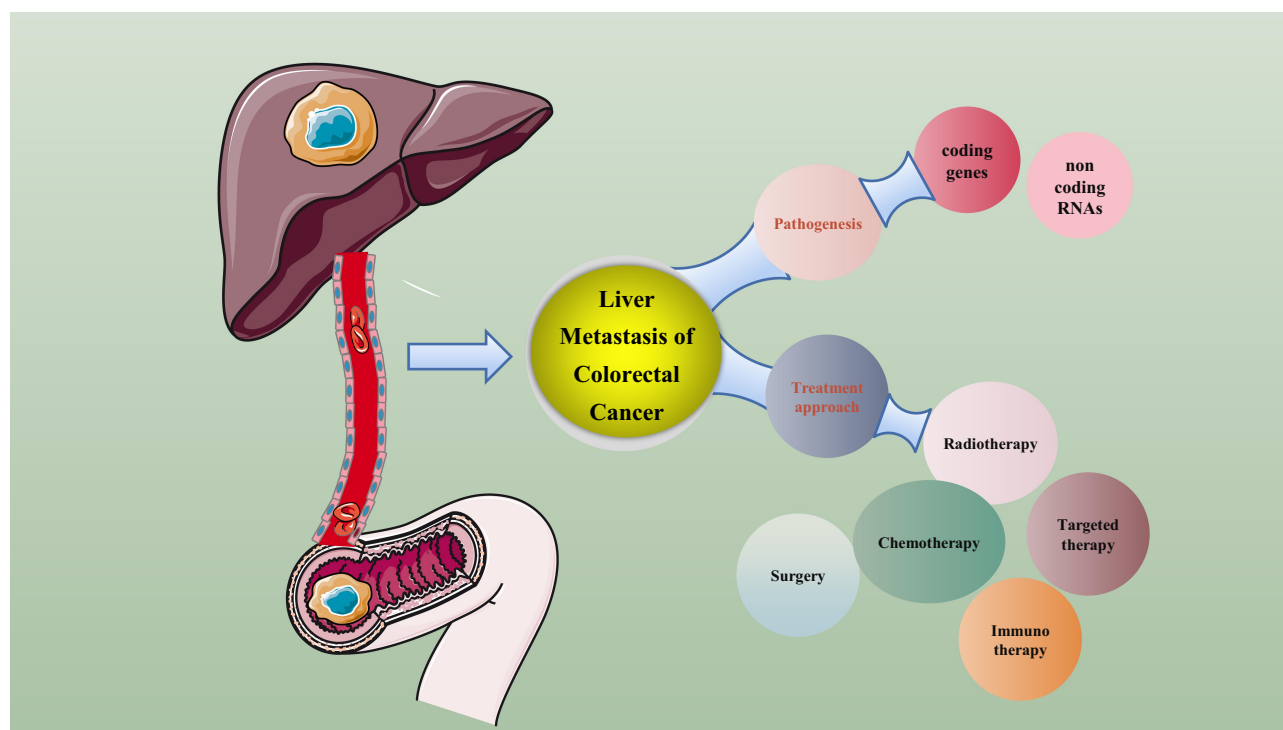
Immunosuppressant therapy is one of the current research hotspots. The target of this treatment is the activation and inhibitory receptors distributed on the surface of T lymphocytes. The activated receptors include CD28, GITR, CD27, etc, and the inhibitory receptors include programmed death 1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), etc. These receptors are also called immune checkpoints. PD-1 is expressed on the surface of immune cells, and programmed cell death ligand 1 (PD-L1) is a tumor cell surface ligand. The surface of solid tumor invading lymphocytes shows PD-1 positive, and PD-1 binds to PD-L1. Inhibit the function of T lymphocytes and induce immune escape of tumor cells. Therefore, blocking PD-1 binding to PD-L1 can reduce tumor cell immune escape.<sup>121</sup> Immunosuppressants against PD-1/PD-L1 that have been marketed include nivolumab, pembrolizumab, and atezolizumab. Relevant studies have shown that immunosuppressive therapy can significantly prolong the median progression-free survival of patients and the advantage of progression-free survival is more prominent.<sup>122</sup> The reason may be that chemotherapy drugs have a fast onset of cytotoxicity, and PD-1 inhibitors are induced by regulating

the immune microenvironment. T cells kill tumor cells, and checkpoint inhibitors work slower than chemotherapy drugs.<sup>123</sup>

Immunotherapy has become a hot spot in current tumor treatment research, and obvious curative effects can also be seen in CRLM. However, there are still some problems: on the one hand, immunotherapy has narrow indications and is not suitable for any cancer patients. It cannot be used by breastfeeding women, organ transplant patients or patients with advanced cachexia; on the other hand, after the use of immunotherapy. Some patients can get obvious relief in a short time, but there are also cases of drug resistance in a short time. These issues still need follow-up research.

## Conclusion and Future Perspectives

Colorectal cancer is still the third largest malignant tumor in the world, and metastasis is the most common cause of death of colorectal cancer, of which liver metastasis is more common. Early diagnosis and treatment of liver metastasis of colorectal cancer is a necessary measure to reduce mortality and improve quality of life and survival time of patients. This paper introduces the research progress of coding genes and ncRNA in the research field of CRLM in recent years, there is an urgent need to understand their mechanism of action in CRLM, looking



**Figure 1** A summary of mechanism and treatment on liver metastasis of colorectal cancer.

forward to finding new early diagnostic indicators, and even guiding clinical treatment. Secondly, multidisciplinary comprehensive therapy is one of the main directions in the clinical treatment of liver metastasis of colorectal cancer in recent years. The comprehensive application of surgical treatment, cryotherapy, radiofrequency ablation, absolute ethanol injection, hepatic artery chemoembolization, portal vein chemoembolization, radiotherapy, laser therapy, liver perfusion therapy and immunotherapy will provide a new opportunity for the prognosis of patients with liver metastasis of colorectal cancer (Figure 1).

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## Disclosure

The authors declare that they have no competing interests.

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