Liver metastasis of colorectal cancer: Mechanism and clinical therapy (Review)

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Abstract. Liver metastasis is a common complication in colorectal cancer (CRC), with its presence and progression significantly shortening patient survival. Therefore, a deeper understanding of the underlying mechanisms driving liver metastasis in CRC is essential to identify more effective and actionable therapeutic targets and improve prognosis. Liver metastasis in CRC is a multifaceted and dynamic process. Tumor cells with invasive properties communicate with the surrounding microenvironment through mechanisms such as immune checkpoint molecules and cytokines, thereby establishing a supportive niche for their colonization and proliferation. Moreover, suppressive immune cells may enhance the invasiveness of tumor cells. The interplay between tumor cells and the microenvironment is an interdependent process. Targeting these interactions offers promising potential for novel therapeutic strategies. The present review outlined mechanisms of colorectal cancer liver metastasis, emphasizing the immune microenvironment's role, current treatment approaches, and future development prospects.

Contents

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1. Introduction

In 2020, colorectal cancer (CRC) is the third most prevalent malignancy globally and the second leading cause of cancer-associated deaths (1) Distant metastasis is a key driver of mortality in CRC, with the liver being the most common site of metastasis (2). A total of 15-25% of patients with CRC present with synchronous liver metastases at initial diagnosis, while a further 15-25% develop metachronous liver metastases following primary CRC resection (2). Currently, a limited number of these liver metastases are amenable to surgical resection, and the 5-year survival rate for these patients is 25-44%. Moreover, up to 60% of patients experience rapid recurrence following resection (3).

The exact mechanisms underlying colorectal liver metastasis (CRLM) remain poorly understood. Tumor cell dissemination from the primary site to distant organs and the subsequent formation of metastatic tumors involve a dynamic process regulated by numerous genes and signaling pathways. This process includes tumor cell detachment from the primary site, entry into the circulatory or lymphatic system, extravasation and colonization at secondary sites. Tumor cell invasion, migration, adhesion, extracellular matrix remodeling, neovascularization and immune regulation are key in facilitating this metastatic cascade. The rise of immunotherapy, with its notable clinical success, has highlighted the critical role of the tumor immune microenvironment (TIME) in CRLM. CRLM represents a complex interaction between tumor and microenvironmental cells. Tumor cells, while acquiring invasive phenotypes, maintain intercellular communication with microenvironmental cells, regulating their functions through both direct and indirect mechanisms. This regulation involves the expression of immune checkpoint molecules and the secretion of cytokines, establishing a microenvironment conducive to tumor cell colonization and proliferation (4). Moreover, suppressive immune cells enhance the invasiveness of tumor cells by activating pro-metastatic signaling pathways. This interaction between tumor cells and the microenvironment drives the development of CRLM (Fig. 1).

2. Acquisition of invasive phenotype of malignant cells

The development, invasion and metastasis of CRC are complex biological processes involving multiple genetic alterations. Successive mutations and abnormal expression of genes such

as APC, KRAS, BRAF and PTEN activate signaling pathways promoting CRC invasion and metastasis (5).

Epithelial-mesenchymal transition (EMT) is a critical precursor to CRLM. EMT refers to the phenotypical transformation of tumor epithelial cells into a mesenchymal phenotype, which enhances their migratory capacity (6). This involves the loss of intercellular junctions, increased secretion of intercellular plasma hydrolases and disruption of apical polarity, resulting in a breakdown of cell-cell adhesion. Concurrently, these changes induce the expression of N-cadherin, vimentin and α-smooth muscle actin, facilitating the transition from polarized epithelial cells to multipolar mesenchymal cells. This transformation increases cell motility, enabling tumor cells to detach from epithelial clusters and migrate individually in a mesenchymal manner, further enhancing the metastatic potential (7). The E-cadherin-β-catenin complex serves a pivotal role in maintaining epithelial integrity. Disruption of this complex leads to the detachment of cells from the primary tumor, enabling invasion and migration through the extracellular matrix and entry into the circulatory or lymphatic system. This is an important initiating step in the development of CRLM (8).

The acquisition of an invasive phenotype in CRC is governed by signaling pathways, including Wnt/β-catenin (9,10), TGF-β (11,12), PI3K/AKT (13-15), MEK/ERK (16,17) and hepatocyte growth factor (HGF)/MET (18). These pathways are regulated by intracellular oncogenes and tumor suppressor genes, as well as tumor microenvironmental signaling factors that influence tumor cell invasion and metastasis (Fig. 2).

3. Remodeling of TIME promotes CRLM

Hepatic susceptibility to colonization by circulating tumor cells compared with other metastasis sites such as the lungs and peritoneum is primarily attributed to its highly permeable blood vessels, unique hemodynamic properties and distinct immune microenvironment. Notably, the ability to tolerate immune responses contributes to the creation of an immunosuppressive microenvironment, which protects the organ from excessive immune reactions to antigens. Additionally, liver homeostasis is maintained by specialized resident cells and diverse immune cell populations, which collectively regulate immune responses and oncogenesis (19-21).

During liver metastasis, immune cells undergo functional changes as a result of communication with tumor cells. Typically, under the influence of tumor cells, immune cells shift toward an immunosuppressive phenotype. Simultaneously, these immune cells reverse their roles to promote the invasive behavior of tumor cells by releasing pro-metastatic cytokines. This facilitates the establishment of a pre-metastatic niche, supporting the colonization of metastatic tumor cells and leading to the formation of metastatic foci (Fig. 3) (22).

T cells. $CD8^+$ T cells play a critical role in antitumor immunity, and their infiltration is associated with a lower risk of recurrence and extended survival in patients with CRLM (23,24). However, tumors employ various mechanisms to suppress $CD8^+$ T cell activity, facilitating immune evasion immune evasion. The expression of immune checkpoint molecules, such as PD-1/PD-L1, has emerged as a significant immunosuppressive factor and a promising therapeutic target (25). Both tumor and stromal cells exhibit high PD-L1 expression, which binds PD-1 on T cells, thereby inhibiting their activation. This interaction converts cytotoxic into exhausted T cells, promoting immune escape (25). Elevated PD-L1 expression in CRC is associated with advanced tumor stage, lymph node involvement, distant metastasis and poor prognosis (26,27). PD-L1 expression in CRLM is notably higher than in primary tumors, suggesting the activity of infiltrating $CD8^+$ T cells in metastases is more significantly suppressed compared with primary foci (28). Aberrant activation of signaling pathways such as Wnt/β-catenin, PI3K/AKT, MEK/ERK and HGF/MET all contribute to the upregulation of PD-L1 expression in tumor cells (29). Targeted inhibition of these pathways, combined with αPD1 therapy, has shown potential in combating CRC liver metastasis (30).

Increased infiltration of $CD4^+$ T cells in CRC has been associated with better prognosis following resection of liver metastatic tumors (31,32). However, different $CD4^+$ T cell subtypes exert varying effects on tumor behavior. $CD4^+$ T cells within the liver tend to differentiate into immunosuppressive phenotypes, producing high levels of immunosuppressive cytokines and restricting immune responses against metastatic tumors in the liver (33). T helper (Th)1 cells enhance the cytotoxic activity of $CD8^+$ T cells, thereby boosting antitumor immunity. Th1 cell infiltration in CRC is associated with improved disease-free survival, while Th17 cell infiltration, which carries immunosuppressive functions, is associated with poor prognosis (34). Th17 cells are predominantly enriched in the primary lesions of metastatic CRC (mCRC) (35). Th17 cells promote tumor growth and metastasis by secreting cytokines such as IL-17, IL-21 and IL-22 (36). Furthermore, Th17 cells release tumor necrosis factor receptor superfamily member 12A, a cytokine that induces EMT and facilitates liver metastasis in CRC (35). The presence of Th17 cells in resected liver metastases is associated with poor prognosis (37).

Regulatory T cells (Tregs), identified by the expression of CD25 and FoxP3, are classical immune suppressors (38). In CRLM, Tregs are the primary source of IL-10, which increases PD-L1 expression on monocytes. This interaction diminishes $CD8^+$ T cell infiltration and impairs antitumor immunity in CRLM (39). Previous studies have shown a significant increase in the proportion of Tregs in both mouse models (39,40) and resected CRLM specimens from patients (41). Furthermore, Treg-mediated suppression of the antitumor immune response is linked to clinical prognosis of patients with CRLM (42). Studies have revealed a paradox where elevated infiltration of $FOXP3^+$ T cells in CRC is associated with improved relapse-free and disease-specific survival, while low $FOXP3^+$ T cell infiltration is associated with poor prognosis (31,43). This discrepancy may be due to the heterogeneity of Tregs within the tumor microenvironment (TME). Saito *et al* (44) identified two distinct subpopulations of Tregs in CRC terminally differentiated immunosuppressive $FoxP3^{high}$ and pro-inflammatory $FoxP3^{low}$ subtypes. Inflammatory Treg-infiltrating CRC showed significant upregulation of genes associated with inflammation and immune responses. Functionally distinct subpopulations of Tregs influence CRC prognosis in opposing directions, with high FOXP3 expression in immunosuppressive Treg-infiltrating tumors associated with poorer outcomes.

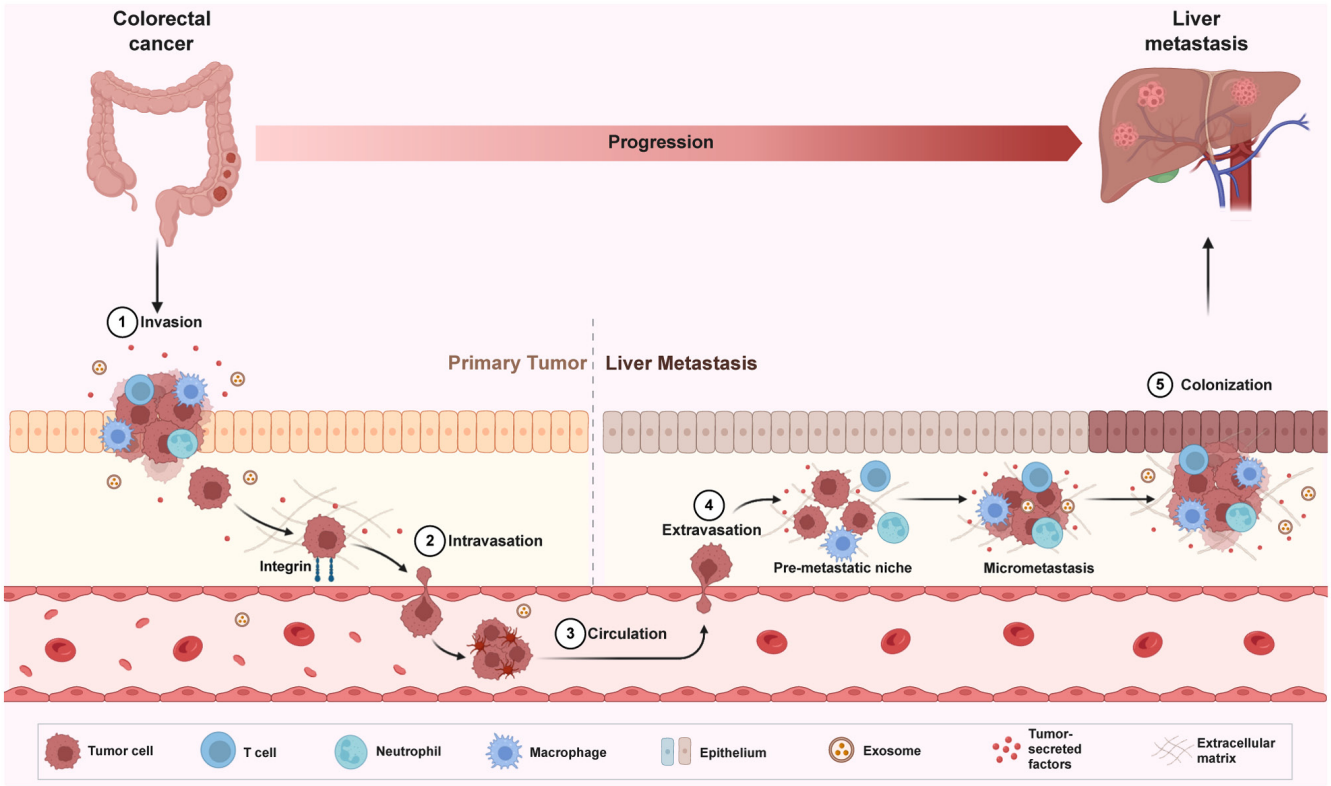

Figure 1. Liver metastasis of colorectal cancer Acquisition of invasive phenotype of malignant cells is the driving force of colorectal liver metastasis. Tumor cells interact with immune cells in the microenvironment to reverse antitumor activity. The immune cells can be re-educated to promote progression and metastasis.

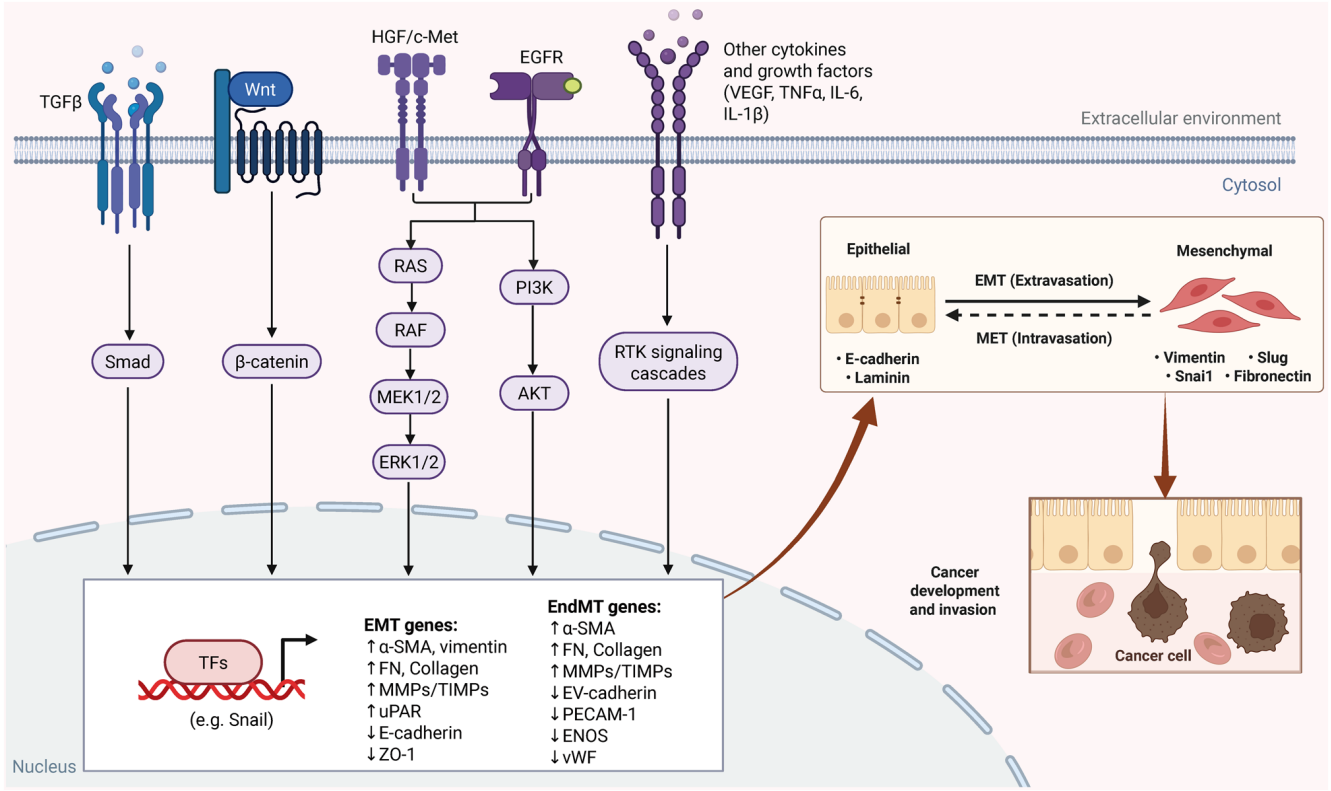

Figure 2. Acquisition of invasive phenotype is regulated by numerous genes and signaling pathways of malignant cells in colorectal cancer. HGF, hepatocyte growth factor; RTK, receptor tyrosine kinase; TF, transcription factor; EMT, epithelial-mesenchymal transition; SMA, smooth muscle actin; FN, fibronectin; TIMP, tissue inhibitor of metalloproteinases; uPAR, urokinase-type plasminogen activator receptor; ZO-1, zonula occludens-1; MET, mesenchymal-epithelial transition.

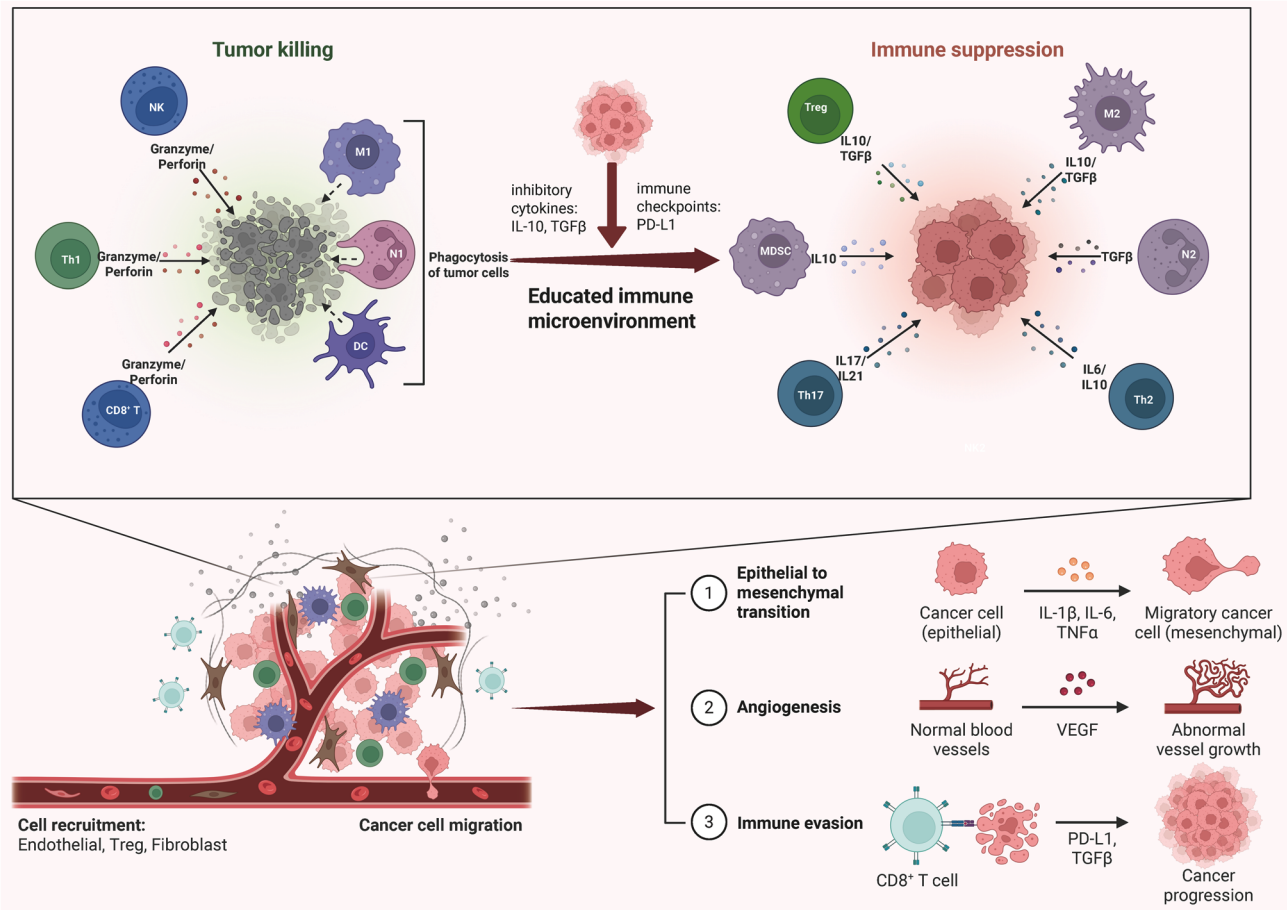

Figure 3. Interactions between tumor cells and microenvironmental immune cells contribute to the enhancement of tumor cell invasiveness. NK, natural killer; Th, helper T cell; DC, dendritic cell; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cells.

Pedroza-Gonzalez *et al* (45) demonstrated that, compared with Tregs from primary hepatocellular carcinoma, Tregs in CRLM exhibit higher expression of glucocorticoid-induced tumor necrosis factor receptor and stronger immunosuppressive activity. These findings suggest that a more precise characterization of Treg subpopulations in CRC and its liver metastases may deepen the understanding of Treg function in CRLM and help refine therapeutic strategies.

Macrophages. Macrophages within the TME exhibit notable plasticity and heterogeneity, classified into M1-type macrophages with pro-inflammatory, immune activating and antitumor properties, and M2-type macrophages, which possess immunosuppressive and pro-tumor functions. M2 macrophages are the dominant subtype in liver metastases (46,47) and associated with poor prognosis (48).

M2 macrophages facilitate tumor invasion and metastasis through several mechanisms, such as remodeling the extracellular matrix (49) and inducing EMT (50,51). Additionally, M2 macrophages contribute to tumor angiogenesis through the secretion of VEGF (52) and support immune evasion by releasing immunosuppressive cytokines such as IL-10 and TGF-β (53). Aberrant expression and activation of signaling molecules such as X-box binding protein 1 (XBP1) in M2 macrophages are further amplified by elevated cytokine secretion of cytokines, including IL-6 and VEGFA, which accelerate CRLM progression (54).

Cytokines and exosomes serve pivotal roles in CRC cells by inducing macrophage polarization toward the M2 phenotype. TGF-β, a classical cytokine, regulates macrophage polarization and, in CRLM, is modulated by pro-oncogenic factors such as collagen triple helix repeat containing 1, which further promotes CRLM by remodeling infiltrating macrophages via TGF-β signaling (55). Additionally, CCL2 is a key regulator of M2-type polarization, which fosters CRLM progression. Pro-oncogenic factors such as STAT3, transcription factor 4 (TCF4) and spondin 2 in CRC cells stimulate CCL2 secretion (56-58). Targeting the CCL2/CCR2 chemokine pathway reduces M2-typetumor-associated macrophages (TAMs) at metastatic sites, disrupts the immunosuppressive TME and enhances the susceptibility of mCRC to antitumor T cell responses (59). Tumor-derived factors such as CCL20, IL-10, VEGF and IL-1β also serve key roles in promoting macrophage infiltration and M2 polarization in CRLM (60,61). Exosome-mediated release of pro-oncogenic factors also contributes to the M2 polarization. CRC cells induce M2 polarization and establish an immunosuppressive pre-metastatic niche via the exosomal release of microRNAs (miRs; such as miR-25-3p, miR-130b-3p and miR-425-5p, miR-21-5p, miR-203, miR-934, miR-135a-5p and miR-106a-5p) and signaling molecules such as heat shock protein 90B1, and circ-0034880, which promote CRLM (62-69).

Recent studies have identified new macrophage subtypes (70,71). Liu *et al* (70) found that complement C1q subcomponent C (C1QC)$^+$ macrophage express genes like CXCL9 and CXCL10, which are associated with favorable responses to immune checkpoint therapy and primarily support cellular phagocytosis and antigen presentation. This suggests that C1QC$^+$ macrophage may have a beneficial role in CRLM treatment. Conversely, secreted phosphoprotein 1(SPP1)$^+$ macrophage exert pro-angiogenic and tumor metastasis-promoting functions, with signature genes associated with poor prognosis. Notably, SPP1$^+$ macrophage are absent in primary hepatocellular carcinoma but significantly enriched in CRLM, suggesting that they may facilitate CRC cell metastasis to the liver (70). Inhibiting their function may benefit CRLM treatment. Wu *et al* (71) demonstrated notable spatial reprogramming of the metastatic microenvironment, particularly involving immune-suppressive cells such as mannose receptor C-type 1$^+$ CCL18$^+$ M2-like macrophages. These macrophages were notably enriched in metastatic tumors and exhibited heightened metabolic activity.

Neutrophils. Neutrophils in the TME exhibit dual roles: In early-stage tumors, they enhance T cell responses, while in advanced tumors, they adopt an immunosuppressive function (72). Similarly to macrophages, neutrophils in the TME can differentiate into distinct subsets, categorized as antitumor N1- and pro-tumor N2-type (73). N1-type neutrophils enhance tumor cell killing by expressing immune-activating cytokines and chemokines while inhibiting arginase expression. TGF-β in the TME induces the polarization of neutrophils from N1 to N2-type. N2-type neutrophils suppress tumor-killing T cell activity (74) and promote tumor invasion and metastasis by stimulating angiogenesis (75).

Neutrophils play a critical role in the formation and progression of CRLM (76). These metastases are characterized by neutrophil infiltration, which is notably more pronounced compared with uninvolved liver tissue. Neutrophils in the metastatic site promote angiogenesis and tumor metastasis by producing high levels of FGF2. Additionally, activated neutrophils can release neutrophil extracellular traps (NETs), and serum NET levels are elevated in patients with CRLM compared with those without liver metastases (77). Furthermore, liver metastasis specimens contain significantly more NETs than primary CRC lesions. NETs trap tumor cells in the liver, enhancing tumor proliferation and invasiveness, thus facilitating liver metastasis formation (78).

Tumor cells induce neutrophil infiltration via multiple pathways. CRC cells secrete granulocyte colony stimulating factor, which recruits neutrophils and upregulates Bv8/Prokineticin 2 expression, promoting immunosuppression and angiogenesis, thereby contributing to CRC metastasis (75,79). Seubert *et al* (80) demonstrated that tumor-derived tissue inhibitor of metalloproteinases 1(TIMP-1) upregulates stromal derived factor-1, recruiting neutrophils to the liver, and promoting liver metastasis. Aberrantly expressed molecules such as cell migration inducing hyaluronidase 1 (81) and DNA rrimase subunit 1 (82) in CRLM ead to the production of CXCL1 and CXCL3, causing accumulation of immunosuppressive neutrophils, ultimately enhancing CRLM progression. These findings suggest potential therapeutic targets for future CRLM research and treatment.

Myeloid-derived suppressor cells (MDSCs). MDSCs, a heterogeneous group of immature myeloid cells, serve a pivotal role in facilitating CRLM by inducing immunosuppression, remodeling the extracellular matrix and promoting angiogenesis (83). Additionally, MDSCs are involved in the formation of NETs within the pre-metastatic niche (84). Abnormal expression and secretion of cytokines trigger MDSC infiltration, further advancing CRLM. CCL2-CCR2 signaling has been shown to induce MDSC infiltration in a STAT3-dependent manner, enhancing their immunosuppressive functions and contributing to CRC progression (85-87). Furthermore, CRC-derived CCL15 (88) and TME-derived CXCL1 (89,90) recruit MDSCs to establish a pre-metastatic niche and promote CRLM. Cytokines such as CCL7 (91), IL-6 (92), IL-33 (93) and exosomes containing long non-coding RNA MIR181A1HG (94) also serve critical roles in inducing MDSC infiltration, enhancing tumor invasiveness, supporting neovascularization and facilitating the creation of a pre-metastatic ecological niche in the liver. Targeted inhibition of these cytokines may offer an effective therapeutic approach for CRLM.

Dendritic cells (DCs). DCs, as antigen-presenting cells, initiate immune responses by capturing exogenous antigens and presenting them to T cells. To evade immune surveillance, tumor cells suppress antigen presentation by releasing inhibitory cytokines such as TGF-β (95). Compared with DCs from healthy individuals, those from patients with CRC exhibit impaired antigen presentation, decreased expression of costimulatory molecules, increased secretion of immunosuppressive IL-10 and reduced levels of immunostimulatory IL-12 and TNF-α (96). Nagorsen *et al* (97) found that tumor-infiltrating S100$^+$ DCs in CRC are negatively associated with systemic antigen-specific T cell responses and positively associated with Tregs. Hsu *et al* (98) discovered elevated CXCL1 expression in CRC patient-derived DCs, which enhanced cell migration, increased matrix metalloproteinase 7 expression and promoted EMT, reflecting the altered functionality of DCs within the CRC TME. Huang *et al* (99) revealed that tumor-associated fibroblasts in CRC secrete WNT2, which suppresses DC function through the JAK2/STAT3 pathway. Targeting WNT2 may restore DC-mediated antitumor immunity. Further exploration of the mechanisms regulating DC function in CRC may identify new therapeutic targets for CRC treatment.

Natural killer (NK) cells. As a key component of innate immunity, NK cells exert antitumor effects by releasing cytotoxic molecules such as TRAIL and FasL. In a mouse model of CRLM, NK cells were shown to inhibit liver metastasis of CRC (100). Increased NK cell infiltration is associated with improved overall survival (OS) in patients with CRLM (101).

Restoring NK cell function inhibits CRLM progression in CRC. Dupaul-Chicoine *et al* (102) demonstrated that the NLRP3 inflammasome suppresses metastatic growth of CRC in the liver by enhancing the tumor-killing activity of NK cells. In NLRP3 inflammasome-deficient mice, IL-18 signaling is impaired, affecting NK cell maturation in the liver

and their ability to effectively kill tumor cells (102). TRAIL is hypothesized to play a central role in NK cell-mediated tumor killing. TRAIL is constitutively expressed on hepatic NK cells and, together with perforin and FasL, triggers a toxic response to tumor cells *in vitro* (103). Neutralizing TRAIL with a monoclonal antibody significantly increases the formation of experimental hepatic metastases (103). CXCR3 has been shown to enhance protection against CRLM by promoting NK cell infiltration and plasticity (104). CXCR3 facilitates the accumulation and persistence of $CD49a^+$ NK cells, which exhibit the highest cytotoxic capacity among metastasis-infiltrating NK cells (104).

However, NK cell function is impaired in both CRC and liver metastases compared with NK cells in healthy livers. CRC cells regulate the TME pH by producing lactic acid, which lowers the pH within NK cells, leading to mitochondrial dysfunction and apoptosis. This enables tumor cells to evade the cytotoxic effects of NK cells (105). Metabolic dysfunction in the metastatic niche notably impacts NK cell functionality. Increased glutamine uptake by cancer cells depletes glutamine availability for NK cells, decreasing their activity and cytotoxicity, thereby promoting CRLM progression (106).

Resident liver cells contribute to the colonization of tumor cells in the liver. Upon entering the portal circulation, tumor cells reach the hepatic sinusoidal capillaries through the portal vein. These tumor cells trigger non-specific liver defense mechanisms, leading to their phagocytosis by resident immune cells such as Kupffer cells (KCs) and NK cells (107).

KCs, the resident macrophages of the liver, serve a pivotal role in maintaining liver homeostasis and are key contributors to the pathogenesis of liver disease. KCs are essential in defending against liver metastasis due to their phagocytic capability, cytokine production and promotion of tertiary lymphoid structures (108). Dysfunction of phagocytosis in KCs is a key driving force in CRLM. Some tumor cells can evade phagocytosis by KCs, highlighting the need for further research into this evasion mechanism to identify novel therapeutic targets for liver metastasis (109). The balance between pro-phagocytic 'eat me' signals, such as tumor-associated antigens, calreticulin, SLAM Family Member 7 and Erythroblast Membrane Associated Protein (ERMAP), and anti-phagocytic 'don't eat me' signals, including CD47, PD-L1, CD24 and β2-microglobulin, is a key determinant in the phagocytosis process (110). Additionally, the functional reprogramming of KCs warrants attention. Following metastatic colonization of the liver, KCs undergo transcriptional reprogramming typical of TAMs, which facilitates tumor progression (111). The phagocytosis of exosomes released by the primary tumor into the circulation and into the liver by KCs can initiate the formation of a pre-metastatic niche in the liver (66).

Liver-resident specialized NK cells also serve a significant role in the early stages of metastasis by contributing to the establishment of pre-metastatic niches. Invariant NK T cells in the liver promote metastasis by producing fibrogenic cytokines such as IL-4 and IL-13, independent of T cell receptor activation, thereby inducing a fibrotic niche in the liver. Targeted disruption of IL-4 and IL-13 signaling pathways in hepatic stellate cells inhibits their trans differentiation into extracellular matrix-producing myofibroblasts, thereby impeding the metastatic proliferation of disseminated cancer cells (112).

Tumor cells that evade innate immune surveillance extravasate from blood vessels and form metastatic lesions. Tumor cell adhesion to the vascular system is not only driven by mechanical blockage of the vasculature, but also by specific cellular adhesion processes that facilitate tumor cell attachment and extravasation (113,114). Liver sinusoidal endothelial cells express the cell adhesion molecule E-selectin, which promotes tumor cell attachment to hepatic sinusoidal endothelial cells. Inhibition of E-selectin effectively decreases the formation of liver metastases (115). Moreover, tumor cells can trigger the release of pro-inflammatory cytokines, such as TNF-α, from KCs, which upregulates the expression of adhesion molecules, such as E-selectin, vascular cell adhesion molecule 1 and intercellular adhesion molecule 1(ICAM1) on hepatic sinusoidal endothelial cells. This increase in adhesion molecule expression enhances tumor cell colonization in the liver (116).

Once tumor cells extravasate into the Disse interstitium, hepatic stellate cells are activated by cytokines such as TGF-β, which is secreted by KCs. This activation prompts hepatic stellate cells to produce extracellular matrix proteins such as collagen, laminin and fibronectin, creating a supportive environment for tumor cell colonization. Additionally, KCs and neutrophils secrete matrix metalloproteinases and elastases, which degrade and remodel the extracellular matrix, facilitating tumor cell invasion. Concurrently, hepatic stellate cells promote a suppressive microenvironment by inducing the apoptosis of cytotoxic T cells and expanding immune-regulatory T cells, creating a favorable environment for tumor cell colonization in the liver (117).

In the context of chronic liver disease, Zeng *et al* (118) observed that abnormal activation of hepatocellular cell cycle-related kinase (CCRK) and NF-κB signaling pathways increases CXCL1 expression, which induces MDSC infiltration and facilitates CRC metastasis to the liver. Non-alcoholic fatty liver disease stimulates KCs to secrete the chemokine CXCL5, which recruits $CXCR2^+$ MDSCs, further promoting CRLM progression (119). Additionally, extracellular vesicles in fatty liver are implicated in promoting CRC liver metastasis by fostering cancer cell proliferation and an immunosuppressive microenvironment through M2 macrophage infiltration, thus enhancing the metastatic TME (120).

4. Current treatment for CRLM

Research into liver metastasis in CRC has revealed numerous potential therapeutic targets, with targeted therapy and immunotherapy emerging as the leading strategies for managing CRLM (121). In addition to traditional neoadjuvant radiotherapy and chemotherapy and adjuvant therapy following surgical resection, integrating targeted and immunotherapies with radiotherapy/chemotherapy and surgery has established a comprehensive treatment system for CRLM (122). This combination therapy offers dual benefits: By initiating neoadjuvant treatment, previously unresectable CRLM can become surgically resectable, increasing the number of patients eligible for hepatic resection while decreasing perioperative

morbidity and mortality (123). Second, these combination therapies show promise in enhancing long-term survival rates for patients (124).

EGFR inhibitors. EGFR , a member of the receptor tyrosine kinase (TK) family, serves a key role in CRC development and invasive metastasis through downstream signaling pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT pathways (125). Cetuximab, the first monoclonal antibody targeting EGFR, significantly improves OS and progression-free survival (PFS) in patients with CRC who are resistant to other treatment (126). When combined with chemotherapy, cetuximab has demonstrated favorable therapeutic outcomes. The combination of cetuximab with FOLFIRI (irinotecan, fluorouracil and leucovorin) significantly decreases the risk of disease progression in patients with mCRC compared with FOLFIRI alone (127). The combination of cetuximab with FOLFOX4(oxaliplatin, leucovorin, and fluorouracil) as first-line treatment for mCRC has also shown superior remission rates compared with the FOLFOX4 regimen alone (128). However, mutations in the RAS gene in CRC confer resistance to cetuximab, meaning cetuximab is effective in patients with RAS wild-type mCRC (129) Another EGFR targeting drug, panitumumab, is a fully humanized antibody that does not induce antibody-dependent cell-mediated cytotoxicity (125). The PRIME trial, which examined the efficacy of FOLFOX alone and in combination with panitumumab in patients with mCRC, found that the combination therapy resulted in higher OS and PFS compared with FOLFOX treatment alone (130,131).

VEGF and its receptor inhibitors. Bevacizumab, a monoclonal antibody targeting the angiogenesis inhibitor VEGF, has received US Food and Drug Administration approval for the treatment of mCRC and demonstrated favorable efficacy (132). A meta-analysis by Cao *et al* (133), which included 1,838 patients with mCRC, showed that chemotherapy combined with bevacizumab following primary tumor resection significantly prolonged OS compared with chemotherapy alone. The study also revealed improved OS in patients who were initially unable to undergo resection of their primary tumor when treated with bevacizumab. Additionally, the combination of bevacizumab with chemotherapy may enhance the resectability of CRLM. In a study by Tang *et al* (134), the combination of bevacizumab with mFOLFOX6 as first-line treatment for patients with unresectable CRLM harboring RAS mutations demonstrated significantly superior efficacy compared with mFOLFOX6 monotherapy. This combination not only markedly increased the R0 resection rate of liver metastases but also improved the overall resectability of liver metastases, leading to improved PFS and OS in patients. Ramucirumab, a VEGFR antagonist that specifically binds VEGFR2 and blocks ligand-receptor binding, has also shown promising results in mCRC treatment (135). In a study by Tabernero *et al* (136), the combination of ramucirumab and FOLFIRI was evaluated against a placebo in patients with mCRC. Ramucirumab and FOLFIRI combination significantly improved OS in patients. Ramucirumab is currently approved for use in the second-line treatment of mCRC.

TK inhibitors (TKIs). Receptor TKs, located on the cell surface and intracellularly, play a key role in intercellular signaling, which influences cell function. TKIs block the activity of kinase proteins that contribute to tumor cell proliferation and the development of tumor vasculature. Regorafenib is an oral, multi-targeted TKI that inhibits VEGFR1-3, PDGFR, FGFR, KIT, RET1 and BRAF and has been shown to improve survival in patients with refractory mCRC (137). Regorafenib is used to treat mCRC that progresses despite previous chemotherapy, anti-VEGF or anti-EGFR therapy (138). In addition to regorafenib, fruquintinib is an oral TKI that selectively inhibits different subtypes of VEGFR, thereby inhibiting tumor angiogenesis and growth (139). The FRESCO study evaluated the effectiveness and safety of fruquintinib as a third-line or subsequent treatment for patients with mCRC. The results demonstrated that fruquintinib monotherapy significantly prolonged survival in patients with mCRC who had failed second-line or higher chemotherapy (140). FRESCO-2, an international, multicentre, randomised, double-blind, phase 3 study, also demonstrated that fruquintinib significantly improved overall survival in patients with refractory metastatic colorectal cancer compared to placebo (141). Fruquintinib is currently approved by FDA for use in patients with mCRC who have previously undergone fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild-type and medically appropriate, an anti-EGFR therapy (142).

Immune checkpoint inhibitors. In recent years, immune checkpoint inhibitors have garnered attention due to their success in achieving long-lasting responses in a range of previously difficult-to-treat solid tumors (143). Overman *et al* (144) demonstrated the significant efficacy of the PD-1 inhibitor nivolumab alone in individuals with deficient mismatch repair/microsatellite instability(dMMR/MSI) CRC in a multicenter phase II clinical trial (CheckMate142). Similarly, the KEYNOTE-177 (145) study showed a significant improvement in PFS in patients with dMMR/MSI mCRC treated with the PD-1 inhibitor pembrolizumab as first-line therapy, compared with standard treatment. PD-1 inhibitors are currently approved by FDA for patients with dMMR/MSI mCRC who experience disease progression following standard chemotherapy (146). This approval highlights their importance as a pivotal immunotherapy approach, particularly for individuals with liver metastases from CRC. However, the efficacy of PD-1 inhibitors varies among patients, and some do not benefit from them. Patients with proficient mismatch repair/microsatellite stability(pMMR/MSS) CRC, which constitutes the majority of the patient population, derive limited benefits from PD-1 inhibitor therapy. For individuals with dMMR/MSI CRC, who are currently considered candidates for PD-1 inhibitor treatment, the observed efficacy rate is suboptimal. In the KEYNOTE-016 trial, pembrolizumab was administered to a cohort of 41 patients with CRC, including both pMMR/MSS and dMMR/MSI subgroups, who experienced disease progression following chemotherapy. In patients with dMMR/MSI CRC, the immune-related objective response rate was 40% and the 20-week PFS rate was 78%. By contrast, patients with pMMR/MSS CRC exhibited an immune-related objective response rate of 0% and a 20-week PFS rate of 11% (147).

Furthermore, liver metastases from CRC induce systemic immune tolerance through a unique immunosuppressive mechanism, which may further affect the efficacy of PD-1 inhibitor therapy (148-150). Exploring effective combination therapies may enhance the efficacy of PD-1 inhibitors. The CheckMate-142 study demonstrated that combining PD-1 inhibitors with CTLA4 inhibitors improves antitumor efficacy (151). In addition to immune checkpoint inhibitors, drugs such as regorafenib have gained widespread attention as potential combination therapies with PD-1 inhibitors due to their promising role in modulating immunity and improving the TME (152,153).

Others. Cancer vaccines, adoptive cell transfer (ACT) therapy and oncolytic viruses have emerged as prominent areas of research in CRLM (154-156). As a form of active immunotherapy, cancer vaccines present the immune system with tumor-specific or -associated antigens, inducing antitumor cytotoxic responses that help the immune system recognize and destroy cancer cells (157). ACT therapy enhances the natural anti-cancer response by activating or genetically modifying autologous or allogeneic immune cells *in vitro* to boost tumor-fighting capabilities, followed by reinfusion into patients. ACT includes therapies such as cytokine-induced killer cells and chimeric antigen receptor T cell therapies (158). Oncolytic virus therapy uses naturally occurring or genetically engineered viruses to selectively target and lyse tumor cells. This strategy not only modulates the TIME but also activates specific anti-tumor immune responses (159). Additionally, it is crucial to explore the role of cytokines, chemokines and adjuvants in enhancing the precision and efficacy of immunotherapies in CRLM.

5. Conclusion

Liver metastasis is a major factor influencing the prognosis of patients with CRC. The process of liver metastasis in CRC is complex and involves interconnected stages. Key pathways that affect the invasive and metastatic potential of CRC cells have been identified, along with prognostic and therapeutic molecules. Additionally, factors within the TME influencing liver metastasis in CRC have been preliminarily analyzed. Notably, the discovery of immune-associated targets holds promise for treating liver metastasis in CRC and improving prognosis. However, the clinical application of these targets and associated drugs in individuals with CRLM remains limited, and many patients do not benefit from current targeted therapies and immunotherapies. Therapeutic strategies aimed at modulating the immunosuppressive microenvironment, such as depleting immunosuppressive cells, inhibiting immune checkpoint pathways and stimulating cytotoxic cells are critical approaches for enhancing the effectiveness of immunotherapy.

Currently, novel immunotherapies for CRLM remain in preclinical or clinical trials, and their successful integration into clinical practice faces challenges. Firstly, CRLM creates a highly immunosuppressive microenvironment within the liver. This hostile TME actively inhibits the function of effector immune cells (such as cytotoxic T cells and NK cells), rendering many immunotherapies ineffective. Secondly, tumor heterogeneity and evolution make it difficult to identify universal therapeutic targets. Thirdly, lack of predictive biomarkers makes it difficult to select patients most likely to benefit from expensive and potentially toxic immunotherapies, leading to low response rates and inefficient resource use. Lastly, overcoming the aforementioned challenges above often requires combining immunotherapies (e.g., dual checkpoint blockade) with other modalities like chemotherapy, targeted therapy (e.g., anti-VEGF, anti-EGFR), radiotherapy, liver-directed therapies (ablation, embolization), or other immunomodulators. Combinations significantly increase the risk of severe immune-related adverse events (irAEs), including hepatitis, colitis, pneumonitis, and endocrine toxicities. Managing overlapping toxicities, especially in patients with liver involvement, is challenging and can limit dosing or lead to treatment discontinuation.

Overcoming these multifaceted challenges requires further intensive studies to understand the CRLM biology and liver immunology, elucidate the underlying mechanisms, discovering robust biomarkers and identify novel therapeutic targets. Deeper understanding of the key molecules and signaling pathways influencing the invasive and metastatic potential of CRC is key, achievable through the integration of high-throughput genomic technology. Considering the complex and heterogeneous influence of the TME on liver metastasis, it is necessary to investigate the functional characteristics and dynamic changes of distinct cell populations throughout the liver metastasis process, at a single-cell level to identify key cells and molecules driving TME remodeling. Moreover, as the understanding of the mechanisms underlying CRLM advances, the diagnosis and treatment of this condition may shift toward a multidisciplinary approach and enhance patient care by facilitating a comprehensive and integrated treatment strategy.

In conclusion, further research is required into the mechanisms in CRLM, the exploration of novel targets for personalized treatment and the development of innovative intervention strategies to improve CRLM therapy efficacy.

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Availability of data and materials

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Authors' contributions

CJY conceptualized the study and wrote the manuscript. LZ performed the literature review. CHW and YJY contributed to conception and design. ZLS revised and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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