Molecular Therapy
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Review

Mechanisms of drug resistance in breast cancer liver metastases: Dilemmas and opportunities

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Breast cancer is the leading cause of cancer-related deaths in females worldwide, and the liver is one of the most common sites of distant metastases in breast cancer patients. Patients with breast cancer liver metastases face limited treatment options, and drug resistance is highly prevalent, leading to a poor prognosis and a short survival. Liver metastases respond extremely poorly to immunotherapy and have shown resistance to treatments such as chemotherapy and targeted therapies. Therefore, to develop and to optimize treatment strategies as well as to explore potential therapeutic approaches, it is crucial to understand the mechanisms of drug resistance in breast cancer liver metastases patients. In this review, we summarize recent advances in the research of drug resistance mechanisms in breast cancer liver metastases and discuss their therapeutic potential for improving patient prognoses and outcomes.

INTRODUCTION

Breast cancer metastasizes mainly through the circulation to the bones, lungs, liver, and brain, with the liver being one of the most common sites for solid metastases. Compared with other sites of frequent metastasis, the liver is one of the most frequent sites of metastatic relapse. The clinical incidence of breast cancer liver metastasis (BCLM) is 40%–50%, and the death rate is 50%–62%.[1] Generally, BCLM patients receiving treatments have a mean overall survival (OS) of 31.0 months.

The development of BCLM is a complex process. In 1889, Stephen Paget proposed the "seed and soil" hypothesis to explain the process, and it is still the accepted model today. Paget compared cancer cells to "seeds" and the destination of cancer metastasis to "soil." He suggested that distant tumor metastasis can only occur if the seeds (disseminated tumor cells) are compatible with the soil (metastatic organs).[2,3] BCLM is regulated by several factors, and the unique tissue structures of the liver and the vascular system play an important role.[4] In addition, inflammatory factors, chemokines, and cell adhesion molecules are also involved (Figure 1).[4] In patients with BCLM, the prognosis is poor and drug resistance is common. Drug resistance can be classified as primary and acquired. As the term indicates, primary resistance refers to cancers evading the initial treatment. After prolonged treatment of tumors that respond to therapy initially, acquired drug resistance develops.[5] The "key determinants" of tumor resistance include tumor burden and growth kinetics, tumor heterogeneity, the physical barriers of the cell membrane, the immune system and microenvironment, undruggable cancer drivers, and the impact of drug pressure.[6] A better understanding of the mechanisms of drug resistance that occur in BCLM patients will allow the development and optimization of treatment strategies. This review summarizes recent advances in the study of drug resistance mechanisms in BCLM and discusses their therapeutic potential for improving the prognosis of patients.

FACTORS CONTRIBUTING TO DRUG RESISTANCE IN BCLM

Unique immune microenvironment

There is a complex interaction between tumor cells and the tumor microenvironment that determines the metastatic tumor phenotype and therapeutic response. The immune microenvironment is composed of immune cells, cytokines, cancer cells, and the extracellular matrix (ECM). All of these play a critical role in the progression of liver tumors and drug resistance.[7] Table 1 summarizes the therapeutic targets of each section and their related studies.

Immunoreactive cells

As an immune organ, the liver is rich in immunoreactive cells, including Kupffer cells, hepatic sinusoidal endothelial cells, hepatic stellate cells (HSCs), pit cells, lymphocytes (e.g., natural killer T cells), gamma-delta T cells, dendritic cells, etc. Moreover, the liver produces immune-related molecules such as C-reactive protein and soluble pattern-recognition receptors, which play a key role in systemic inflammation and immunity (Figure 2).[28]

Although the liver is rich in immune cells, it has a unique immunotolerant microenvironment due to its embryonic origin as a hematopoietic organ, the flow of portal blood from the portal vein into the liver from the gastrointestinal tract and spleen, and mucosal immunity from the biliary system through the excretion of metabolites. Unlike normal capillary endothelial cells, hepatic sinusoidal endothelial cells do not have a basement membrane. This facilitates the exchange of substances between hepatocytes and blood, and lymphocytes are in direct contact with hepatocytes. Because the liver is constantly exposed to bacterial components and dietary antigens flowing from the gastrointestinal tract through the portal vein. It is necessary that

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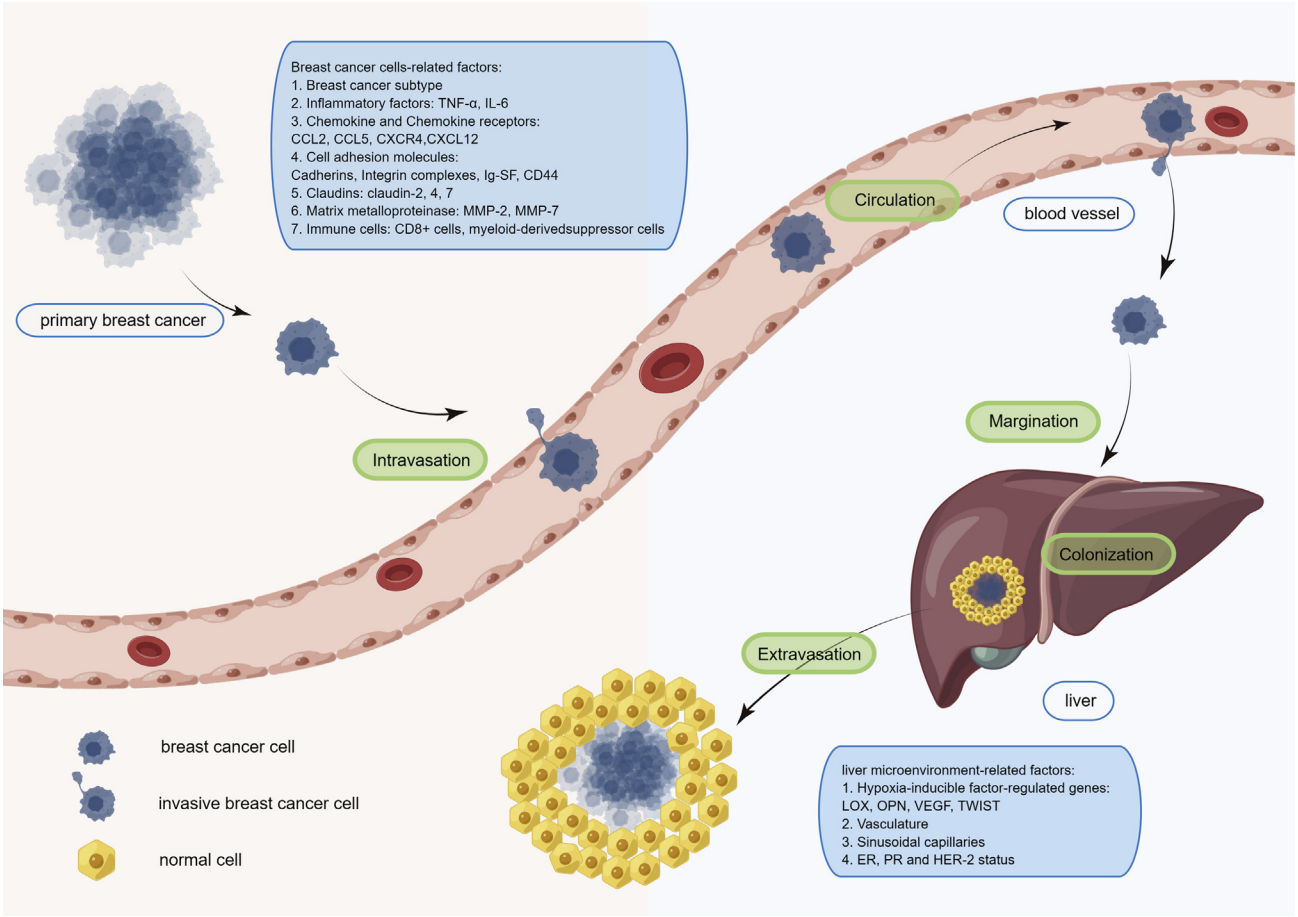

Figure 1. Schematic diagram of the process of tumor metastasis from breast to liver

Intravasation: breast cancer cells invade the blood circulation through the endothelium of tumor vessels. Circulation: breast cancer cells survive in the vasculature. Margination: circulating breast cancer cells arrest at the liver site by adhering to the sinusoidal endothelial cells via specific adhesion molecules. Extravasation: breast cancer cells migrate through sinusoidal endothelial cells, migrate into the liver, and finally proliferate there. Breast cancer cells survive and form micrometastatic foci in the liver microenvironment.

the liver maintains a level of tolerance that balances the elimination of bacterial pathogens and avoids excessive inflammation caused by the nonpathogenic intestinal environment, thus resulting in a unique immunotolerant microenvironment.[28]

An experiment conducted in mice has demonstrated that the resistance of liver tumors to anti-programmed cell death protein 1 (PD-L1) antibody therapy was largely due to the unique immunotolerant microenvironment of the liver and was independent of the tumor origin or type.[29] In addition, using multiple mouse models, Yu et al. have found that the liver metastases siphon activated CD8+ T cells from the systemic circulation.[30] As a result of their interaction with FasL+CD11b+F4/80+ monocyte-derived macrophages, activated antigen-specific Fas+CD8+ T cells undergo apoptosis in the liver.[30] Thus, in preclinical models, liver metastases create a systemic immune desert.[30] Through CD8+ T cell deletion, liver metastases also have been demonstrated to exploit host peripheral tolerance mechanisms to cause acquired immunotherapy resistance.[30] Hepatocellular carcinoma (HCC)-derived exospheric plant homeodomain and ring finger domain 1 (HRF1) promotes immune escape and PD1 resistance to programmed cell death protein 1 (PD-1) immunotherapy by upregulating T cell immunoglobulin and mucin domain 3 (TIM3) expression in natural killer cells through degradation of miR-449c-5p.[31] Moreover, liver-directed radiation therapy in combination with immunotherapy can promote systemic antitumor immunity.[30] It is interesting to note that treatment with targeted PD-1 monoclonal antibody has shown some promise in treating primary HCC despite the poor results of immunotherapy for liver metastases. In May 2020, the combination therapy of tecentriq, which targets PD-L1, combined with avastin was approved for clinical use by the US Food and Drug Administration.[32] Cabozantinib, keytruda, nivolumab, and nivolumab in combination with ipilimumab are currently approved as second-line treatments for HCC.[33] Furthermore, Hu et al. have revealed that the combination of interferon-α and anti-PD-1-based immunotherapies shows promising anticancer effects in HCC patients. And they have suggested a

Table 1. BCLM therapeutic targets

Section	Target	Study	Research subjects	Reference
Immune microenvironment	CXCR4	an open label, phase Ib/II trial to study the safety, tolerability and anti-tumor activity of X4P-001 in combination with toripalimab in patients with locally advanced or metastatic TNBC	human	NCT05103917
		a phase 1 study to evaluate the pharmacokinetics and safety of MB1707 in patients with advanced cancer	human	NCT05465590
		aHSC-secreted chemokine CXCL12 induces NK cell quiescence through its cognate receptor CXCR4 to suppress NK cell-sustained breast cancer dormancy	mice	Correia et al.[8]
	CXCR3	IP-10 (CXCL10) can trigger emergence of dormant breast cancer cells in a metastatic liver microenvironment	*ex vivo* hepatic MPS	Clark et al.[9]
	PD-L1	seed- and soil-dependent differences in murine breast tumor microenvironments dictate anti-PD-L1 IgG delivery and therapeutic efficacy	mice	Liu et al.[10]
	CTLA-4	phase I/II randomized study of NBTXR3 activated by Abscopal or RadScopal radiation in combination with immunotherapy (anti-CTLA-4 and anti-PD-1) for patients with advanced solid malignancies	human	NCT05039632
	CD47	a phase 1, open-label, multicenter, dose escalation study evaluating the safety, tolerability, and preliminary efficacy of IMM2902 in patients with HER2-expressing advanced solid tumors	human	NCT05076591
	CCDC25	DNA of neutrophil extracellular traps promotes breast cancer metastasis to liver	mice	Yang et al.[11]
	a-UPR	ErSO, a small-molecule activator of the unfolded protein response eradicates human breast tumors in mice	mice	Boudreau et al.[12]
	STAT3	combined inhibition of JAK2-STAT3 and SMO-GLI1/tGLI1 pathways inhibits breast cancer metastasis to the liver and lung	mice	Doheny et al.[13]
		simultaneous inhibition of breast cancer and its liver and lung metastasis by blocking inflammatory feedforward loops	mice	Lu et al.[14]
	GATM/MPS1	creatine promotes breast cancer metastasis to the liver by activating Smad2/3	mice	Zhang et al.[15]
	IL-6	nobiletin inhibits breast cancer liver metastasis by suppressing the IL-6-	mice	Wu et al.[16]

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Table 1. *Continued*

Section	Target	Study	Research subjects	Reference
		induced ERK-STAT and JNK-c-JUN pathways		
Metabolic reprogramming	Myc	phase 1/2 open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of OTX-2002 as a single agent and in combination with standard of care in patients with hepatocellular carcinoma and other solid tumor types known for association with the MYC oncogene	human	NCT05497453
	PI3K	SOX2-OT induced by PAI-1 promotes TNBC cells metastasis to liver and lung by sponging miR-942-5p and activating PI3K/Akt signaling	Mice	Zhang et al.[17]
	PKM2	circular RNA KIF4A promotes liver metastasis of breast cancer by reprogramming glucose metabolism	Mice	Huang et al.[18]
	AKT	dietary alterations modulate the microRNA 29/30 and IGF-1/AKT signaling axis in breast cancer liver metastasis	Mice	Shastri et al.[19]
Extracellular vesicles	MMP	microenvironment-induced TIMP2 loss by cancer-secreted exosomal miR-4443 promotes liver metastasis of breast cancer	Mice	Wang et al.[20]
Tumor vascular	EGF	phase I trial of cetuximab and erlotinib (EGFR inhibitors) and SIR-Spheres (yttrium microspheres) in patients with advanced malignancies and liver metastases	human	NCT01432119
EMT	TGF-β	fresolimumab and radiotherapy in metastatic breast cancer	human	NCT01401062
	CXCR4	the FUS/circEZH2/KLF5/feedback loop contributes to CXCR4-induced liver metastasis of breast cancer by enhancing EMT	Mice	Liu et al.[21]
	cytoskeleton-associated proteins	lovastatin inhibits EMT and metastasis of TNBC stem cells through dysregulation of cytoskeleton-associated proteins	mice	Zheng et al.[22]
Others	circROBO1	circROBO1 facilitates the carcinogenesis and liver metastasis of BC through the circROBO1/KLF5/FUS feedback loop, which inhibits the selective autophagy of afadin by suppressing the transcription of BECN1	mice	Wang et al.[23]
	S100A10	S100A10 functions as a metastasis promoter of breast CSCs by conferring both invasion ability and CSC properties in breast cancers	mice	Yanagi et al.[24]
	Notch1	ezrin accelerates breast cancer liver metastasis through promoting furin-like convertase-mediated cleavage of Notch1	mice	Chen et al.[25]

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Table 1. *Continued*

Section	Target	Study	Research subjects	Reference
	AGR3	anterior gradient 3 promotes breast cancer metastasis to liver and bone and chemotherapy response	human	Xu et al.[26]
	ER	estrone, the major postmenopausal estrogen, binds ERa to induce SNAI2, epithelial-to-mesenchymal transition, and ER+ breast cancer metastasis	mice	Qureshi et al.[27]

CXCR4, C-X-C chemokine receptor type 4; TNBC, triple-negative breast cancer; aHSC, activated hepatic stellate cells; CXCL12, C-X-C motif chemokine ligand 12; NK, natural killer; CXCR3, C-X-C motif chemokine receptor 3; CXCL10, C-X-C motif chemokine ligand 10; MPS, microphysiological systems; PD-L1, programmed cell death-ligand 1; IgG, immunoglobulin G; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CD47, cluster of differentiation 47; HER2, human epidermal growth factor receptor 2; CCDC25, coiled-coil domain containing 25; DNA, deoxyribonucleic acid; UPR, unfolded protein response; STAT3, signal transducer and activator of transcription 3; JAK2, Janus kinase 2; SMO, smoothened; GLI1, GLI family zinc finger 1; GATM, glycine amidinotransferase; MPS1, mucopolysaccharidosis 1; IL-6, interleukin-6; ERK, extracellular regulating kinase; JNK, Jun N-terminal kinase; PI3K, phosphatidylinositide 3-kinase; SOX2-OT, SOX2 overlapping transcript; PAI-1, plasminogen activator inhibitor-1; PKM2, pyruvate kinase isozyme type M2; IGF-1, insulin-like growth factors 1; MMP, matrix metalloproteinase; TIMP2, TIMP metallopeptidase inhibitor 2; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor β; FUS, fused in sarcoma/translocated in liposarcoma; KLF5, KLF transcription factor 5; CSC, cancer stem cell; AGR3, anterior gradient 3; ER, estrogen receptor; SNAI2, snail family transcriptional repressor 2.

mechanism involving the synergistic effect of interferon-α and anti-PD-1 antibodies in HCC; they propose that the combination therapy remodels the tumor-immune microenvironment by inducing CD27+CD8+ T cell infiltration, which subsequently causes HCC tumor regression.[34] In addition, combination immunotherapy has shown potential in a variety of tumors. Presently, the combination of PD-1 antibody and cytotoxic T lymphocyte-associated antigen-4 antibody has been approved for the treatment of some cancers. For example, nivolumab combined with ipilimumab has been approved for melanoma, non-small cell lung cancer, HCC, and renal cell carcinoma.[35–38] Combination immunotherapy may also be a promising new direction for the treatment of BCLM; therefore, its role in BCLM deserves further exploration. However, it is worth noting that patients receiving immune combination therapy may experience higher rates of grade 3–4 toxicity, and there have been several immune combination therapy clinical trials that have been discontinued for this reason.[39] Considering the special role of the liver in drug metabolism, the potential for significant immune-related toxicity must be taken into account when exploring immune combination therapy in BCLM. Vascular endothelial growth factor (VEGF), the most established biological mediator of tumor angiogenesis with concomitant immunosuppressive effects, is a cytokine induced by local tissue hypoxia and acidosis that promotes the growth of defective and leaky tumor vessels.[40] VEGF has direct local and systemic immunosuppressive effects in addition to indirect effects on anti-tumor immunity through its effect on blood vessels by impeding tumor infiltration of immune effector cells.[41] The anti-VEGF therapy reverses the immune suppressive effects of VEGF, which is associated with increased infiltration of regulatory cells, myeloid-derived suppressor cells, and M2 type tumor-associated macrophage (TAMs) into tumors.[42–45] Moreover, it has been found that targeting PD-1 in conjunction with VEGF inhibition can effectively treat liver metastases. Researchers have found that blocking VEGF reduced the number of PD-L1+ and TIM3+ infiltrating T lymphocytes in a mouse model of colorectal cancer liver metastasis.[44] Furthermore, mice subcutaneously injected with colon cancer cells did not show a significant anti-tumor effect when PD-L1 alone was blocked. But they did show a significant reduction in tumor burden when the treatment was combined with VEGF inhibitors.[44] This suggests that VEGF-A-producing liver tumors may benefit from association of anti-angiogenic molecules with immunomodulators of inhibitory checkpoints. Non-coding ribonucleic acids such as microRNA (miRNA)-934 induce differentiation of TAM to the M2 phenotype, thereby promoting tumor progression and metastasis and mediating therapeutic resistance.[46,47]

Glucose-regulated protein 78 (GRP78) belongs to a group of highly conserved heat shock proteins. It has important stress-response functions and is involved in the unfolded protein response (UPR) and endoplasmic reticulum stress responses as well as cellular metabolism, hypoglycemia, hypoxia, acidosis, viral infection, and deoxyribonucleic acid (DNA) damage repair.[48] It also has been demonstrated that the overexpression of cell surface (CS) GRP78 *in vitro* promotes the invasiveness of breast cancer tumor cells and enhances their colonization and proliferation in the liver.[48] Moreover, GRP78 expression is associated with cancer cell invasion and drug resistance.[49] A signaling network called the UPR is activated in cancer cells by endoplasmic reticulum stress pathways. GRP78 increases chemoresistance of tumors by regulating UPR.[50] GRP78 reduces insulin-like growth factor binding protein 3 entry into cells and promotes breast cancer tumor progression.[51] Tseng et al. found that the C-terminal domain of CS-GRP78 could lead to tamoxifen resistance in breast cancer through activation of signal transducer and activator of transcription 3 (STAT3).[52] The above evidence suggests that GRP78 may be responsible for the development of drug resistance in BCLM. Although it is generally believed that GRP78 influences tumor progression and the therapeutic response by regulating the function of immune cells found in the tumor microenvironment, the exact mechanism remains to be elucidated.

Tumor stroma

In addition to immune cells, the tumor stroma is also an important component of the microenvironment of liver metastases. Cancer-associated fibroblasts (CAFs) are the most abundant cells in the

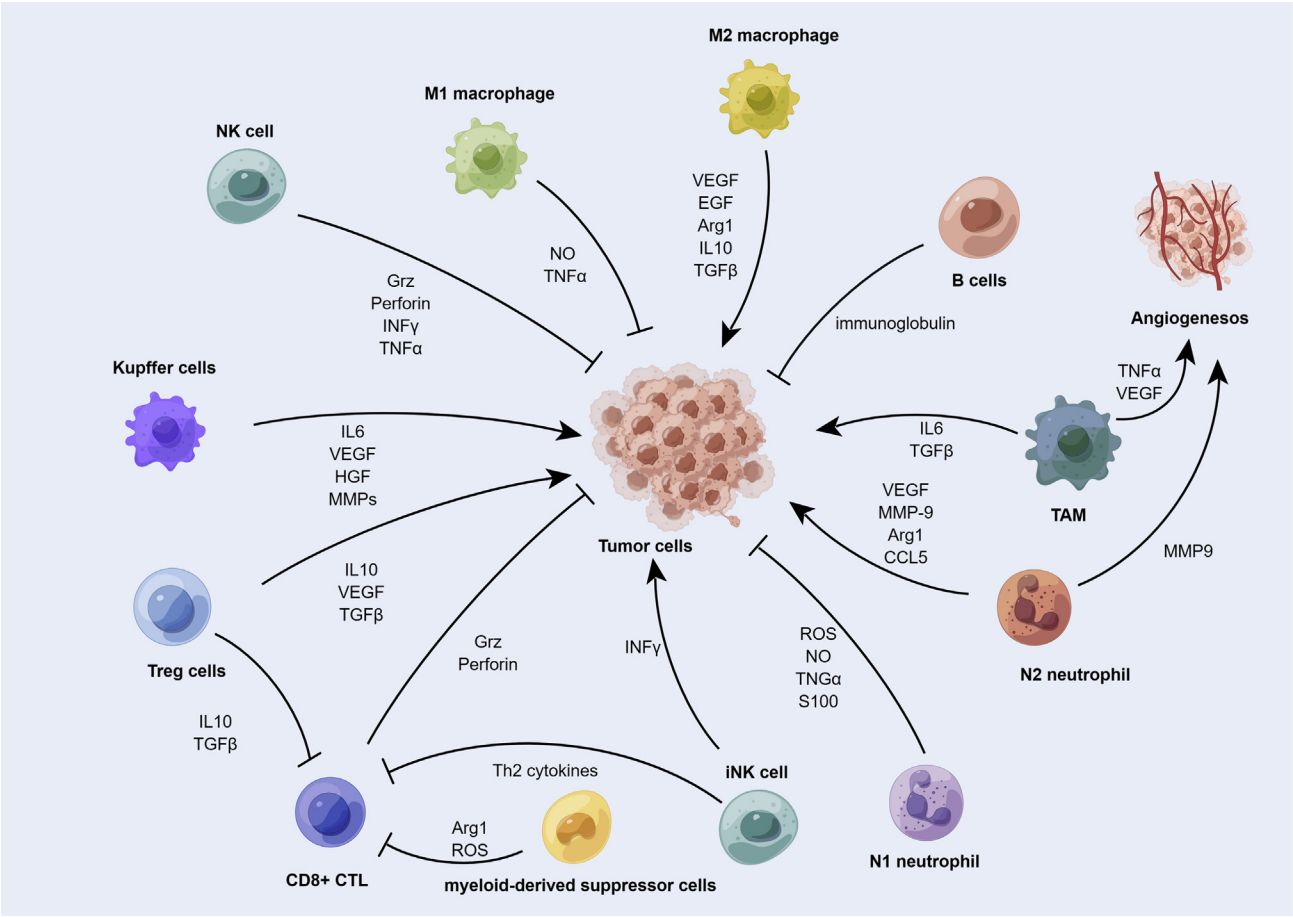

Figure 2. Immune microenvironment of liver metastases

Schematic representation of the interactions between cancer cells, various immune cells, and soluble factors that mediate these cellular interactions. Arrows and blunt ends indicate promotion and inhibition, respectively.

tumor microenvironment and are a key source of the ECM, which constitutes the desmoplastic stroma. CAFs regulate cancer occurrence, progression, metastasis, and tumor resistance to therapy by remodeling the reactive tumor stroma and paracrine actions. The CAFs found in stroma-rich liver metastases mainly originate from HSCs. It has been demonstrated that CAFs/activated HSCs confer chemoresistance and radio-resistance to liver metastases.[53] CAF-secreted exosomes significantly increase miR-92a-3p levels in tumor cells, thereby activating the Wingless/Integrated (Wnt)/β-catenin pathway and directly inhibiting F box and WD repeat domain containing 7 and modulator of apoptosis 1. Ultimately, mitochondria-associated apoptosis is inhibited, thereby promoting tumor progression and chemoresistance.[54] Cancer stem cells (CSCs) also play a key role in drug resistance. A study in mouse models found that the transcription factor nuclear factor erythroid 2-related factor 2 promotes the release of the nuclear cytokine interleukin-33 (IL-33) from CSC, thereby promoting the differentiation of macrophages with a high affinity for the immunoglobulin E receptor FcεRIα. These macrophages can send paracrine transforming growth factor β (TGF-β) signals to the CSC, leading to tumor progression and drug resistance.[55] Aberrant activation of the phosphatidylinositide 3-kinase/protein kinase B (PI3K/PKB) signaling pathway in CSC leads to upregulation of adenosine-triphosphate (ATP)-binding cassette transporter protein expression, which promotes chemotherapeutic drug efflux and leads to drug resistance.[56] Anticancer drugs are likely made ineffective by the abnormal ECM composition and structure in solid tumors. Among the ECM proteins, collagen is the most abundant structural protein in the liver. Disproportionate collagen concentrations can cause an altered cell phenotype and a distorted structure with an abnormal blood flow in the liver.[57] In addition, the high collagen content is a key barrier to drug penetration through the ECM-associated interstitial protein, which can lead to a poor drug distribution and reduce the efficacy of chemotherapeutic agents.[58] Alternatively, by activating multiple mechanotransduction pathways, the ECM stiffness influences tumor metastasis, growth, and drug resistance. In breast cancer, ECM rigidity promotes epithelial-mesenchymal transition (EMT) and metastasis via the twist family BHLH transcription factor

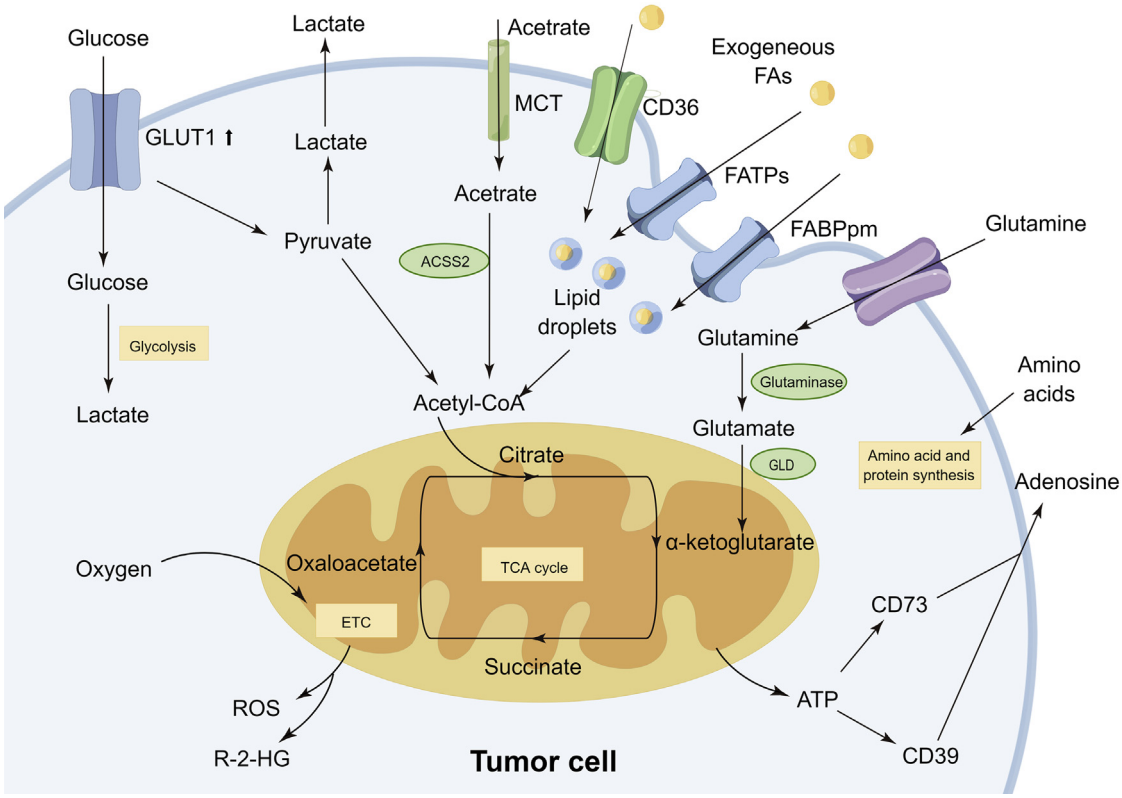

Figure 3. Metabolic reprogramming of liver metastases

To meet the energy and material base required for rapid proliferation of tumor cells, tumor metabolism is abnormally active, and metabolic reprogramming occurs in glucose metabolism, amino acid metabolism, and lipid metabolism.

1-Ras-GTPase activating protein SH3 domain-binding protein 2 pathway.[59] The rigidity of the ECM also promotes the expression of angiogenesis-related factors in cells, such as VEGF-A, hypoxia-inducible factor-1α, and TGF-β1.[60] Moreover, the results of a recent study show that an ECM-derived mechanical signal can upregulate nuclear-enriched abundant transcript 1 (NEAT1) expression. And NEAT1 can promote sorafenib resistance by enhancing autophagy-related protein 3 expression and autophagy.[61,62]

Chemotherapy and radiotherapy disrupt the tumor microenvironment and induce the production of senescence-associated secretory phenotypes (SASPs).[63] Stromal cells in the tumor microenvironment can rapidly enter the aging stage during chemotherapy with production and release of large amounts of SASP factors. Among them, serine protease inhibitor Kazal type 1 can activate cancer cells remaining after treatment and make them resistant to the drug.[64]

Metabolic reprogramming of the liver microenvironment and metastatic foci

Energy metabolism

Cancer cells exhibit significant metabolic plasticity and, when distant metastasis occurs, they adapt to the new metastatic environment by reconnecting metabolic pathways (Figure 3).[65]

Metabolic reprogramming of carbohydrates plays an important role in drug resistance of BCLM. Glycolysis is inhibited in normal mammalian cells under aerobic conditions. However, Warburg found that HCC cells have more active glycolytic activity than normal hepatocytes, and he proposed that malignant tumor cells are equally active in glycolysis under adequate oxygen. This metabolic feature of aerobic glycolysis is called the Warburg effect. It is characterized by high glucose uptake, active glycolysis, and a high lactic acid content of metabolites.[66,67] The Warburg effect explains the phenomenon that tumor cells consume sugar during proliferation without being efficiently productive: under aerobic conditions, cancer cells switch from aerobic phosphorylation to aerobic glycolysis. The more glucose is ingested, the more lactic acid is produced.[68] This mechanism allows tumor cells to adapt to transient or permanent hypoxic conditions and contributes to the production of nucleotides and amino acids.[68] At the same time, the lactic acid produced during this process can promote tumor invasion and contribute to cell migration, angiogenesis, immune escape, and radioresistance.[69] Interestingly, a recent study has shown that, in liver metastases from colon cancer, chemotherapy induced a metabolic shift from glycolysis to oxidative phosphorylation via the sirtuin 1/peroxisome proliferator-activated receptor-gamma coactivator-1 alpha axis, which increased cellular resistance to chemotherapy.[70] Zuo et al., reported

a fasting-mimicking diet has been demonstrated to block a glucose surge and reduce glycogen accumulation in the liver, so it may improve the therapeutic effect of fulvestrant in BCLM patients.[71]

In addition to carbohydrate metabolism, reprogramming of amino acid metabolism has an irreplaceable role in tumor development and drug resistance. Glutamine metabolism can provide materials for over-activated glycolysis and oxidative phosphorylation in tumor cells, and can also induce resistance to chemotherapeutic agents by promoting metabolic homeostasis.[72] A glutamine-targeted cancer metastasis therapy in mice has shown that metabolic therapy targeting glutamine metabolism can control liver metastatic tumors.[73] Wei et al. found that sorafenib resistance in HCC is linked to phosphoglycerate dehydrogenase, the first enzyme in the serine synthesis pathway.[74] These studies have revealed resistance to treatment of liver metastasis as well as improved survival through inhibition of dynamic metabolic mechanisms, suggesting new therapeutic ideas. Nevertheless, there are few studies on metabolic interventions, and their effects on endocrine therapy have not been fully explored. Therefore, further experimental research is required.

The liver is the center of fat metabolism. Excessive accumulation of adipose tissue in the liver is strongly associated with a high risk of metabolic diseases, such as insulin resistance, dyslipidemia, and nonalcoholic fatty liver disease, and may even lead to cancer. Adipocytes play an important role in the tumor microenvironment by secreting adipokines, which influence cancer progression, metastasis, and chemoresistance through multiple signaling pathways.[75] The fatty liver environment can enable metastatic HCC to acquire resistance to antiangiogenic drugs by activating lipid-dependent metabolic pathways.[76]

Effect of metabolic reprogramming on the immune microenvironment

Metabolic alterations in tumors affect the immune microenvironment by affecting immune cells, creating an immunosuppressive environment and thus hindering the effect of immune checkpoint inhibitors in BCLM. On the one hand, the metabolic reprogramming of tumor cells competes with immune cells to consume nutrients.[77] While, on the other hand, they secrete various metabolites. These metabolites act as soluble signaling molecules that can mediate the interaction of tumor cells with the immune microenvironment and reshape the tumor immune microenvironment.[78] For example, by competitive uptake of glucose, tumor cells can suppress both the functions of T cells and the activation of dendritic cells.[79] The key enzyme of glycolysis, pyruvate kinase M2, decreases the number of M1 macrophages, and it increases the proportion of M2 macrophages by promoting tetramer formation.[80] In addition, excess lactate causes intracellular acidification of natural killer cells and promotes apoptosis.[81] The reprogramming of amino acid metabolism leads to a scarcity of the corresponding amino acids in the tumor microenvironment, such as tryptophan and arginine, resulting in the impaired function of immune effector cells.[82,83] Moreover, high levels of fatty acids in the tumor microenvironment contribute to the production of regulatory T cells. This induces the conversion of infiltrating myeloid cells to an immunosuppressive and anti-inflammatory phenotype (Figure 4).[84] Therefore, the combination of inhibitors that target tumor metabolism and immune checkpoint inhibitors may be a promising therapeutic direction to overcome drug resistance in BCLM patients. However, the specific mechanisms of tumor metabolism affecting immune cells still need to be further explored. The primary challenge of combination immunotherapy is to find tumor cell-specific metabolic pathways and metabolites as targets for targeted therapy and to determine the balance between tumor suppression and immune cell activity by exploiting differential metabolic plasticity.

Role of extracellular vesicles

Extracellular vesicles refer to various vesicular structures surrounded by a membrane that are released by cells; they can be divided into four major categories according to their origin and diameter: microvesicles, exosomes, apoptotic bodies, and oncosomes.[85] The composition of extracellular vesicles is highly dependent on the origin cell and contains DNA, RNA, lipids, metabolites, and cell surface proteins.

Microvesicles

Microvesicles, also known as extracellular granules, are formed on the surface of the cell membrane by outward budding and range from 100 to 1,000 nm in diameter; in addition, they are characterized by the prominent exposure of phosphatidylserine residues and other markers on the outer surface.[86] Tumor-derived microvesicles are involved in the survival of tumor cells through intercellular communication. By sending paracrine messages between different cells, microvesicles are able to regulate the tumor microenvironment.[87] Moreover, Ali et al. have demonstrated that HCC cell-derived microvesicles can induce sorafenib resistance both *in vivo* and *in vitro* by activating the hepatic growth factor (HGF)/Ras (a major active pathway in cancer) signaling pathway and by increasing the activity of Forkhead box protein M1, which is one of the proteins actively involved in cell proliferation. Furthermore, they have revealed that the degree of resistance depends on the aggressiveness of the tumor from which the particles originated. In other words, the more aggressive the tumor is, the stronger the tumor growth that the derived particles can support.[88]

Exosomes

Exosomes are small vesicles secreted by cells that mediate signal transduction between neighboring or distant cells.[89] In addition, the formation of a premetastatic niche is an important step in liver metastasis, and tumor-derived exosomes play an important role in this step.[90]

Tumor-derived exosomes play a crucial role in the drug resistance of liver metastases. Tumor-derived exosomes can directly promote the proliferation of liver endothelial cells. They can increase angiogenic activity and are highly resistant to angiogenesis inhibitors as well as chemotherapeutic agents.[91] Moreover, high levels of miRNAs in

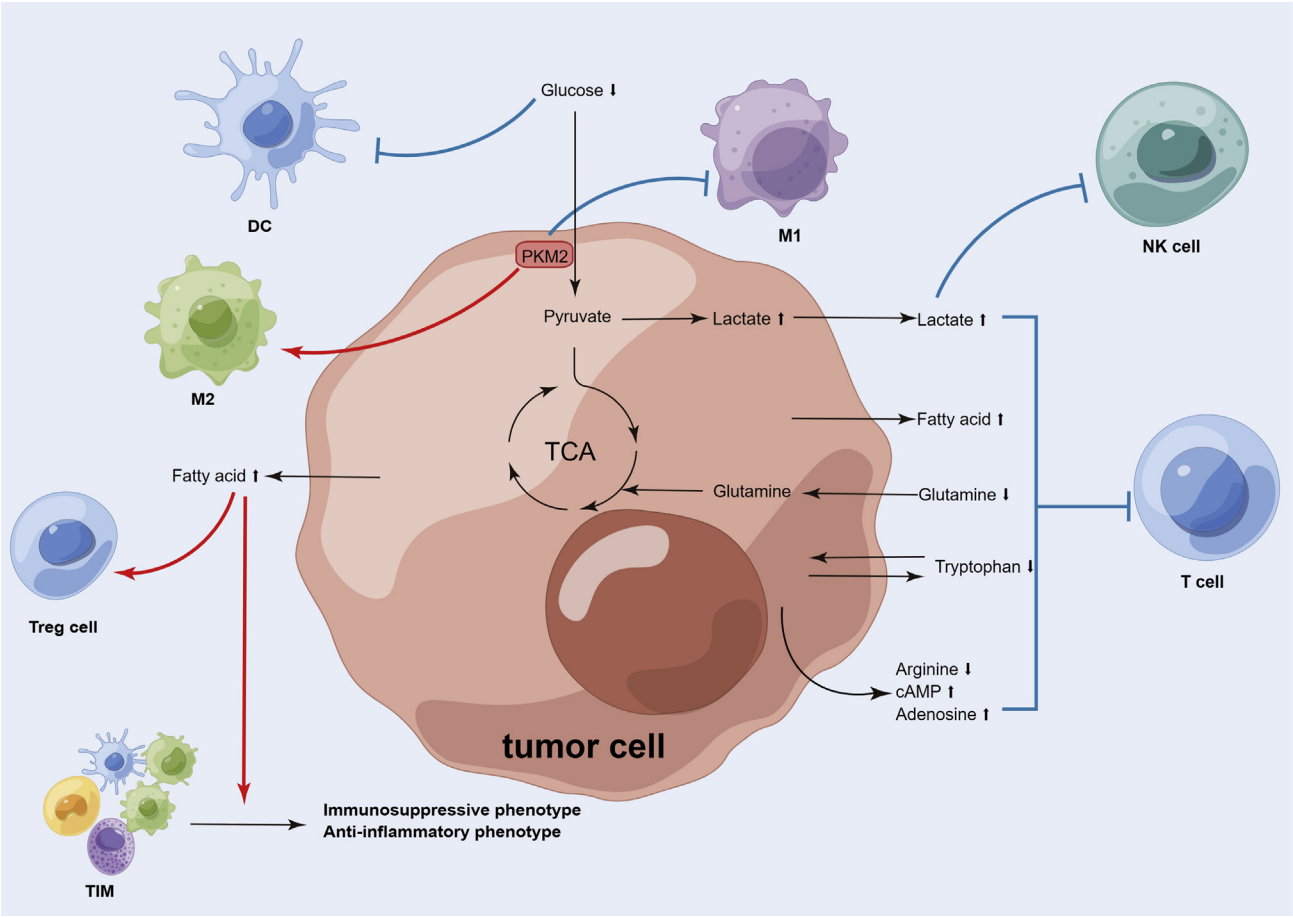

Figure 4. Effect of metabolic reprogramming on immune cells

Alterations in certain metabolic pathways cannot only provide advantageous conditions for tumor cell survival and development, but, in addition, changes in the tumor microenvironment caused by tumor metabolism can affect the function of anti-tumor immune cells and immunosuppressive cells, leading to tumor immune escape.

exosomes have been shown to play a key role in the immune system and mediate drug resistance in liver metastases.[92] For example, miR-1247-3P converts normal fibroblasts into CAFs by inhibiting β-1,4-galactosyltransferases III. In addition, activation of the β1-integrin-NF-κB signaling pathway in fibroblasts enhances secretion of IL-6 and IL-8 as well as promoting chemoresistance in HCC.[93] Exosomes can also mediate chemoresistance between different HCC cell populations. For instance, exosomes secreted by HCC cells have been shown to promote sorafenib resistance both *in vivo* and *in vitro*, and the effect of exosomes from highly aggressive HCC cells was more pronounced than those from less aggressive cells; a possible molecular mechanism involves the intercellular transmission of HGF and subsequent activation of the HGF/c-mesenchymal epithelial transition factor (MET)/Akt signaling pathway.[94] Another possible mechanism of drug resistance may involve the genetic material in tumor-derived exosomes. For example, dysregulated long intergenic nonprotein coding RNA of regulator of reprogramming (linc-ROR) in human hepatocellular carcinomas cells has been demonstrated to cause chemoresistance in HCC. And sorafenib exposure has been shown to increase linc-ROR in HCC cells, HCC-derived exosomes, and exosome-treated receptor cells.[95] Similarly, chemotherapeutic stress (e.g., sorafenib, camptothecin, and doxorubicin) has been shown to result in the upregulation of the long intergenic nonprotein coding RNA of very-low-density lipoprotein receptor (linc-VLDLR) in exosomes.[96] Furthermore, the delivery of linc-VLDLR by exosomes has been demonstrated to increase the expression of ATP-binding cassette, subfamily G member 2.[96] It causes insufficient toxicant concentrations to be exported through the drug, leading to the development of drug resistance.[97]

Apoptotic body

Cells undergoing apoptosis release vesicles that are sized between 50 and 500 nm in diameter, and these vesicles are known as apoptotic bodies. The main physiological role of apoptotic bodies is to clear dead cells to avoid inflammatory responses, but it also has been reported that apoptotic bodies are involved in intercellular communication and can influence tumor progression. Zhao et al. have suggested that intercellular delivery mediated by apoptotic bodies can

be used to enhance drug penetration and tumor destruction. They have demonstrated that apoptotic bodies can carry the remaining drug to neighboring tumor cells after apoptosis and be efficiently delivered to internal tumor cells. This mechanism points to a promising new direction for drug delivery in tumor therapy, but its application in BCLM patients requires further experimental research.[98]

Tumor vascular remodeling and vascular mimicry

Drug biodistribution through the cardiovascular system and drug extravasation/permeation in the tissue microenvironment are critical for the delivery of chemotherapeutic or immunotherapeutic agents to cancer cells within a tumor.[99] Many drugs take advantage of the characteristics of capillary beds in primary tumors; however, small metastatic tumors may not have a vascular system, so drug delivery is therefore impeded. Several studies have observed that the establishment of micrometastatic foci may alter liver perfusion. It has been shown that a 500-μm-sized metastasis in the rat liver reduces liver perfusion by 25%.[100] The results of microcirculation simulations performed in a mouse model with BCLM also suggest that newly established small liver metastases may alter local microcirculation in the nearby liver lobules and their surrounding tissues. These changes may also lead to inadequate tumor perfusion.[101] In addition, studies conducted in mouse models of BCLM have demonstrated that the tumor capillaries do not function properly due to an impaired blood flow, which fundamentally prevents drug penetration into the metastatic tumors.[102] The study of microcirculation in metastases is still in its infancy. Researchers have a limited understanding of how microcirculatory foci alter hepatic perfusion and how drugs are delivered through microcirculation. One of the reasons may be that metastatic cancer cells metastasize to the liver via the portal vein and stay in the microvascular bed. A large number of small thrombi appear in the portal vein, resulting in an increase in the resistance of the microvascular bed and the blockage and disappearance of the small portal veins and capillaries around the tumor sites.[103] We assumed that certain factors secreted by tumor cells and their surrounding tissues may also be responsible for the decrease in blood flow, but this has not been confirmed. Many studies are based on the assumption that drugs can reach metastases unimpeded; therefore, the challenges of drug delivery have been ignored, resulting in limited therapeutic efficacy, drug resistance, and poor clinical benefit.

Another possible cause of drug resistance in BCLM patients is vessel co-option. Studies focusing on the vascularization of metastases have shown that metastases can also be vascularized by vessel co-option; therefore, the cancer cells do not induce new blood vessel growth but rather merge existing blood vessels in the surrounding tissue.[104] This vessel co-option is widespread in BCLM, and it is believed that this may explain the poor clinical benefit of angiogenesis inhibitors, which are often resistant in BCLM patients.[105] In addition to micrometastatic foci and vessel co-option, the unique properties of vascular mimicry make it a possible factor for tumor resistance. The vasculogenic mimicry process occurs in many malignant tumors and is different from the traditional angiogenetic process involving the vascular endothelium. The intricate interactions among vascular mimicry, activation of EMT, and proliferation of CSCs jointly influence tumor invasion and progression, leading to drug resistance in tumors.[106] When antiangiogenic drugs are applied, they promote the formation of vascular mimicry. The increase in vascular mimicry not only leads to drug resistance but also increases tumor invasion and metastasis. This mechanism points to a new approach for treating BCLM that involves both inhibition of angiogenesis and inhibition of vessel co-option with vascular mimicry.

Absence of therapeutic targets and generation of drug-resistant mutations

The absence of a therapeutic target can lead to resistance of drugs targeting the relevant target. C-X-C motif chemokine receptor 2 (CXCR2) is a G protein-coupled receptor that interacts with a variety of chemokines.[107,108] Activation of cellular pathways involving CXCR2 is critical for the development of tumors with metastatic phenotypes. Several experiments demonstrated the potential of CXCR2 antagonists for the treatment of metastatic tumors,[109] and a clinical trial is underway to test this conjecture; the CXCR1/2 inhibitor repertaxin has been proven to be well tolerated in phase I trials and is currently being evaluated for its efficacy in breast cancer patients (NCT012001974).[110] However, in an experiment exploring the extracellular and intracellular mechanisms affecting macrophage inflammatory protein-2 secretion in mice, breast cancer cells that had metastasized to the brain, liver (4TLM), and heart were assessed for CXCR2 expression levels; the levels were lower in the cells that had metastasized to the liver than in the cells that had metastasized to the brain or heart, suggesting that liver metastatic cells may be resistant to the antitumor effects of CXCR2 antagonists.[111]

Certain genetic mutations can also lead to drug resistance. Pan et al. have recently reported a case of a BCLM patient who was resistant to olaparib and camrelizumab. Breast cancer susceptibility gene (*BRCA1*) revertant mutations were detected in this patient, who harbored a heterozygous germline *BRCA1* exon 7–8 deletion. Sequence analysis revealed that this mutation rearranged the reading frame of *BRCA1*, and the researchers concluded that this unique *BRCA1* revertant mutation was associated with drug resistance.[112] In addition, Xu et al. have reported a case of a BCLM patient with a phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) mutation detected in liver metastatic tissue, and this mutation might have led to resistance to the PI3K inhibitor alpelisib (BYL719) in the patient.[113] Besides, estrogen receptor 1 (ESR1) mutations in breast cancer are thought to be one of the mechanisms of drug resistance to aromatase inhibitors. Moreover, ESR1 mutations have been confirmed to be associated with liver metastasis, especially the Y537S and D538G mutations, which are significantly associated with liver metastasis.[114–116] Furthermore, acquired secretory mutations of the *ESR1* gene have been identified in metastatic lesions in patients receiving endocrine therapy.[114,117] Erb-B2 receptor tyrosine kinase 2 (ERBB2) amplification is one of the common mechanisms of resistance to tyrosine kinase inhibitors (TKI). Gene amplification leads to abnormal human epithelial growth factor receptor-2 (HER2) signaling, resulting in activation of the RAS-MEK-ERK signaling pathway, thereby weakening the effect

of epidermal growth factor receptor (EGFR) blockade.[118] MET gene amplification activates the EGFR-dependent ERBB3 phosphorylation and downstream PI3K/PKB signaling pathway, thereby avoiding EGFR-TKI targets and resulting drug resistance.[119] Mutation of the MET kinase structural domain D1228N leads to sustained activation of phosphorylated MET protein. This in turn leads to abnormal activation of the MET signaling pathway, ultimately leading to drug resistance.[120] When the MET 14 exon jump mutation occurs, the binding site for Y1003 and C-CBL E3 ubiquitin ligase will be missing. This results in reduced receptor ubiquitination, impaired MET protein degradation, and continued activation of the proto-oncogene MET, leading to drug resistance.[121] C797S is a key site for the binding of EGFR proteins to ATP-competitive targeting inhibitors. The C797S mutation disrupts the binding of EGFR proteins to third-generation targeted drugs, thereby failing to prevent the binding of EGFR proteins to ATP and the activation of downstream signaling pathways. This leads to resistance to third-generation EGFR inhibitors.[122] Functional defects in PTEN are correlated with drug resistance in HCC. miR-552 negatively regulates PTEN expression at the gene and protein levels in liver tumor-initiating cells, thereby activating phosphorylation of AKT and inducing drug resistance.[123] Some researchers have suggested that PTEN is a tumor suppressor that inhibits PI3K activity. PTEN deficiency promotes the production of immunosuppressive cytokines in tumors, leading to reduced tumor T cell infiltration and decreased drug resistance.[124] The interaction between tyrosine kinase receptor Tie2 and fibroblast growth factor receptor 1 (FGFR1) increased Aurora-A expression and led to aberrant activation of the Aurora-A/Polo-like kinase 1 (PLK1)/cyclin-dependent kinase 1 (CDK1) signaling pathway. The interaction between Tie2 and FGFR1 increased Aurora-A expression and led to aberrant activation of the PLK1/cell-cycle protein-dependent kinase 1 (CDK1) signaling pathway. This is the major contributor to PI3K inhibitor resistance.[125] Saito et al. found that solute carrier family 7 member 5 (SLC7A5) protein was expressed at higher levels in tamoxifen-resistant ER+ breast cancers, and its increased expression level could cause the cells to take up more leucine. The lower levels of leucine inhibited cell division in ER+ breast cancer cells, which may be one of the mechanisms that make ER+ breast cancer resistant to tamoxifen.[126] Tamoxifen also binds and activates ER36 through upregulation of aldehyde dehydrogenase 1 A1 expression, leading to metastasis and drug resistance in breast cancer cells.[127]

The progression of a tumor can also be affected by certain drugs. In fact, steroid receptor turnover has been observed in about 30% of breast cancer patients treated with steroids and specific loss of progesterone receptor. This is an endoplasmic reticulum target, and its absence can lead to drug resistance.[128,129]

Important pathways of intercellular interactions are represented in the genomes of liver metastases that are both enhanced and repressed, and changes in their expression levels may also lead to drug resistance. In a study of BCLM patients, researchers have found that the mTOR pathway was elevated at the transcriptional level in the liver metastases compared with the primary tumor, and activation of the mTOR pathway has been demonstrated to be associated with endocrine therapy resistance.[130,131] The cyclin (*CCN*) gene is a key factor in cell-cycle regulation, and *CCN* amplification is one of the most frequent alterations in cancer, with unique biological relevance.[132] Schwaederlé et al. have identified an extended co-amplification network with FGFR1 as one of the driver genes. Furthermore, the amplification and overexpression of this receptor are associated with a poor prognosis and endocrine resistance in breast cancer patients.[133] In addition, it has been reported that the amplification of *CCND1* is associated with endocrine drug resistance in breast cancer patients.[134] The correlation of the amplification of *CCND2* and *CCND3* and liver metastasis of tumors also has been confirmed in several studies.[134,135] The entire *CCN* amplification network has considerable biological significance, and the gene products within the network may act synergistically during tumor progression to promote tumor development and generate drug resistance.[133]

EMT

EMT is a process by which epithelial cells lose cell polarity and cell-cell adhesion caused by downregulation of the epithelial cell adhesion molecule E-cadherin.[136] It is also one of the major mechanisms in the development of drug resistance in cancer treatment.[136] Researchers believe that EMT enables tumors to evade apoptosis and senescence signals through embryonic signaling pathways.[137] In addition, immediate and widespread EMT in mouse models of colorectal liver metastasis and mouse models of orthotopic breast cancer has been observed. This process involves all surviving tumor cells and responds to multiple antitumor treatments including chemotherapy, thermal ablation, and anti-angiogenic therapy; thus, EMT plays a central role in treatment failure.[138] This may partly explain why immunotherapy for metastatic liver cancer is ineffective but for primary HCC can achieve some efficacy. It also has been shown that tamoxifen-resistant breast cancer cells gain motility and aggressiveness through EMT.[139,140] Moreover, the Notch4/STAT3 signaling pathway plays an important role in this process; therefore, researchers believe that Notch4 may be a therapeutic target for tamoxifen resistance.[141]

N-Cadherin is also involved in EMT and is associated with an enhanced invasive potential of tumor cells.[142] Its expression is positively correlated with metastasis in breast cancer patients; thus, N-cadherin is one of the therapeutic targets in metastatic breast cancer.[143] However, significantly lower N-cadherin levels have been observed in exosomes from 4TLM cells, and it has been speculated that N-cadherin may not be required for 4TLM cell invasiveness and that BCLM patients may be resistant to treatments targeting N-cadherin.[144]

PROSPECTS AND PERSPECTIVES

The clinical treatment of patients with metastatic breast cancer has tremendously advanced in recent years. However, the treatments and drugs currently used rarely target metastatic sites specifically, and tumors remain resistant to combination therapies and become more aggressive when resistance occurs because of the overactivation of compensatory pathways. In addition, many conventional therapeutic agents used to treat liver metastases may quickly fail due to their unique vascular system and enhanced metabolism, and patients

Table 2. Clinical trials for BCLM

Clinical trial number	Official title	Phase	Study population	No. of patients	Study intervention	Primary outcome
NCT03256344	a phase 1b study of talimogene laherparepvec in combination with atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases	1	TNBC or colorectal cancer with liver metastases	36	talimogene laherparepvec vs. atezolizumab	DLT
NCT01862900	phase I/II study of stereotactic body radiation therapy to metastatic lesions in the liver or lung in combination with monoclonal antibody to OX40 (MEDI6469) in patients with progressive metastatic breast cancer after systemic therapy.	1	BC with liver metastases or lung metastases	14	15 or 20 or 25 Gy to liver or lung metastases and MEDI6469 following radiation and on days1, 3, and 5	DLT
NCT05263869	an open-label, multi-center, single-arm phase II clinical study to evaluate the efficacy and safety of MRG002 in advanced HER2-positive breast cancer patients previously treated with trastuzumab and TKIs (Magic-009)	2	BC with liver metastases	99	MRG002	ORR
NCT03500380	a randomized, controlled, multi-center phase II clinical study to evaluate the efficacy and safety of recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate for injection in the treatment of HER2-positive locally advanced or metastatic breast cancer and phase III clinical study to evaluate the efficacy and safety of recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate for injection in the treatment of HER2-positive advanced breast with liver metastases	2/3	HER2+ BC with or without liver metastases	301	RC48-ADC vs. lapatinib + capecitabine	PFS
NCT01437007	a phase 1 dose escalation study of hepatic intra-arterial administration of TKM 080301 (lipid nanoparticles containing siRNA against the PLK1 gene product) in patients with colorectal, pancreas, gastric, breast, ovarian, and esophageal cancers with hepatic	1	inoperable cancer with liver metastases	54	TKM-080301	MTD; DLT
NCT05303038	a phase II clinical study of cryoablation combined with tirelizumab and bevacizumab in liver metastatic triple-negative	2	TNBC with liver metastases	15	cryoablation + tirelizumab + bevacizumab	ORR

(*Continued on next page*)

Table 2. *Continued*

Clinical trial number	Official title	Phase	Study population	No. of patients	Study intervention	Primary outcome
	breast cancer patients failed by multiline therapy					
NCT05325528	an exploratory study of tislelizumab in combination with oxaliplatin and tegafur for the treatment of gastric cancer with liver metastases	2/3	liver metastases	40	tislelizumab + oxaliplatin + tegafur	ORR
NCT05098847	a phase II study of cryoablation combined with sintilimab plus lenvatinib in previously treated unresectable liver metastasis from solid tumors (CASTLE-04)	2	liver metastases	25	cryoablation + sintilimab + lenvatinib	ORR
NCT04714983	a phase I safety and window-of-opportunity study of preoperative intratumoral injection of OX40-ligand expressing oncolytic adenovirus (DNX-2440) in patients with resectable liver metastasis	1	resectable multifocal ($\geq$2 lesions) liver metastasis	30	DNX-2440	MTD
NCT04832204	an exploratory study of apatinib combined with SHR-1210 as second-line treatment in solid tumors with only liver metastases	2	solid tumors with only liver metastasis	20	apatinib and camrelizumab for injection	PFS
NCT05643417	a single center, multi cohort, phase I basket trial of the safety and efficacy of camrelizumab in combination with bevacizumab and HAIC for metastatic liver cancer after standard treatment failure	1	metastatic liver cancer	80	HAIC + bevacizumab + camrelizumab	AEs; TRAEs; SAEs; ORR
NCT04714983	a phase I safety and window-of-opportunity study of preoperative intratumoral injection of OX40-ligand expressing oncolytic adenovirus (DNX-2440) in patients with resectable liver metastasis	1	resectable multifocal ($\geq$2 lesions) liver metastasis	30	DNX-2440	MTD
NCT04832204	an exploratory study of apatinib combined with SHR-1210 as second-line treatment in solid tumors with only liver metastases	2	solid tumors with only liver metastasis	20	apatinib and camrelizumab for injection	PFS

TNBC, triple-negative breast cancer; BC, breast cancer; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitors; ORR, objective response rate; MMAE, monomethyl auristatin E; PFS, progression-free survival; MTD, maximum tolerated dose; PLK1, Polo-like kinase 1; HAIC, hepatic arterial infusion chemotherapy; AEs, adverse events; TRAEs, treatment-related adverse events.

with BCLM are highly susceptible to drug resistance. Immunotherapy, which has shown some effectiveness in HCC of primary origin, has demonstrated unsatisfactory results in the treatment of liver metastases; therefore, the mechanisms need to be further explored. Studies on the causes of drug resistance in BCLM are limited, and few clinical trials have investigated organ-specific metastases. This significantly affects the OS and quality of life of BCLM patients. Table 2 provides a summary of relevant recently completed and ongoing clinical trials about BCLM.

Liver function is sensitive to the tumor load and the type of cancer therapy, and extensive liver metastases can impair liver

function, leading to jaundice, coagulation disorders, and/or ascites, as well as accompanying debilitating effects. Nevertheless, liquid biopsies, tumor-specific biomarkers, and new imaging techniques have the potential to facilitate the early detection of liver metastases. The further development of the standard care for BCLM patients is also needed. Future research directions should consider exploring whether there are specific molecular biomarkers of BCLM that can serve as potential targets for systemic therapy. Furthermore, optimization of hepatic drug delivery by altering the chemical structure of known drugs or the route of administration should be performed.

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AUTHOR CONTRIBUTIONS

Conception and design, X.-H.Z. and C.-Y.Y.; administrative support, X.-H.Z.; collection and assembly of data, all authors; manuscript writing: all authors; final approval of manuscript, all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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