Cancer Management and Research

Elevate Series

Open Access Full Text Article

REVIEW

Angiogenesis and Immunosuppressive Niche in Hepatocellular Carcinoma: Reshaping Vascular - Immune Axis to Potentiate antiPD - 1/PD - L1 Therapy

Wei Li, Gen-Cong Li, Cui-Song Luo, Qiang-Feng Yu, Min Cui

The Department of Hepatobiliary & Pancreatic Surgery, Zhuhai People's Hospital (Zhuhai Clinical Medical College of Jinan University), Zhuhai, People's Republic of China

Correspondence: Wei Li, Department of Hepatobiliary & Pancreatic Surgery, Zhuhai People's Hospital (Zhuhai Clinical Medical College of Jinan University), No. 79 Kangning Road, Zhuhai, People's Republic of China, Email derekweil@163.com

Abstract: Hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related death worldwide, and its complex tumor microenvironment (TME) presents significant challenges for the treatment of this disease. In recent years, tumor immunotherapy has emerged as one of the most successful strategies in cancer treatment, especially for advanced HCC. Programmed cell death protein-1 (PD-1) inhibitors have moderate efficacy as monotherapies for HCC. Tumor angiogenesis, a crucial factor in tumor growth and proliferation, plays a pivotal role in the immune regulation of HCC. The vascular and immune microenvironments of solid tumors engage in dynamic reciprocal crosstalk, forming a complex vascular–immune axis that critically shapes antitumor immune responses and drives therapy resistance. The high degree of angiogenesis observed in HCC leads to abnormal vascular structure and function, which not only promotes tumor growth but also induces hypoxia and acidosis within the TME, thereby suppressing the immune response through various mechanisms. Given the regulatory role of tumor blood vessels in the immune system, the integration of antiangiogenic therapy into current immunotherapy approaches provides a novel treatment option. This integration involves the inhibition of tumor angiogenesis, improvements in the TME, and enhancements of the immune response, among other mechanisms. This review summarizes the angiogenic mechanisms of HCC, the clinical applications of immunotherapy and the regulatory effects of angiogenesis on the immune response in HCC.

Keywords: hepatocellular carcinoma, angiogenesis, tumor microenvironment, PD-1/PD-L1, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) represents the sixth most prevalent malignancy globally and ranks as the third leading cause of cancer-related mortality,[1] imposing a substantial burden on public health systems. Accounting for over 90% of primary liver tumors[2] HCC arises predominantly in the context of chronic liver disease driven by risk factors including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, excessive alcohol consumption, and non-alcoholic steatohepatitis (NASH). Global incidence exhibits significant geographic heterogeneity, with the highest rates observed in East Asia and sub-Saharan Africa, largely attributable to the endemicity of HBV and HCV[3] Projections indicate a continued rise in HCC incidence over the next three decades,[4] necessitating regionally tailored prevention strategies. The therapeutic landscape for unresectable HCC has evolved substantially, progressing from conventional chemotherapy to targeted therapies (notably anti-angiogenic agents) and, more recently, combination immunotherapy. While immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have demonstrated significant advancements in the systemic management of HCC, clinical benefit remains limited, with only a subset of patients responding.[5] The tumour micro-environment (TME), characterized critically by its vascular compartment, plays a pivotal regulatory role in shaping immunotherapy response. Consequently, elucidating the dynamic interplay between immune cells and the tumor vasculature holds promise for enhancing therapeutic efficacy.

Received: 1 May 2025
Accepted: 18 August 2025
Published: 29 September 2025

Vascular-Immune Microenvironment in HCC

HCC is a hypervascular tumor in which angiogenesis serving as a prognostic indicator in occurrence and progression.[6,7] The angiogenic switch is initiated under pathological conditions by excessive proangiogenic factors, such as vascular endothelial growth factor (VEGF)[8] and angiopoietin-1 (Ang-1),[9] which respond to hypoxia inducible factors (HIFs).[10,11] The unsatisfactory therapeutic effect of antiangiogenic therapy in HCC is due to the rapid formation of new collateral circulation. The vasculature in HCC patients exhibits a chaotic pattern of disorganization[12] and lacks normal control mechanisms.[13] Capillarization in the hepatic sinusoidappear as tortuous, dilated, arteriovenous shunts[14] and are hyper-permeable with pericyte detachment.[15] Morphological abnormalities are often accompanied by functional deficiency, which leads to increased interstitial fluid pressure (IFP); this increased IFP compromises transvascular transport, which becomes an obstacle for the penetration of small-molecule agents or lymphocytes into tumors.[16,17]

The immunologically cold phenotype of HCC, marked by inadequate cytotoxic lymphocyte infiltration and intrinsic resistance to immune checkpoint blockade (ICB), is intimately associated with pathological neoangiogenesis. Aberrant tumor vasculature functions as a biophysical barrier,[18] spatially restricting cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells from penetrating neoplastic parenchyma. VEGF orchestrate dual immunosuppressive mechanisms: direct impairment of dendritic cell (DC) antigen-presenting capacity[19] and recruitment of immunoregulatory cellular cohorts, notably $FoxP3^{+}$ regulatory T cells (Tregs)[20] and protumorigenic M2 macrophages.[21] Furthermore, hypoxia-driven stabilisation of HIF-1α establishes a feedforward immunosuppressive loop via transcriptional upregulation of programmed death ligand 1 (PD-L1),[22] effectively subverting T cell receptor-mediated tumor cell recognition. These interconnected vascular-immune dysregulation mechanisms perpetuate therapeutic resistance through both spatial exclusion of effector immune populations and molecular reprogramming of the tumor microenvironment (TME). Therefore, combined therapeutic strategies targeting vascular normalization and immune activation (eg, anti-angiogenic agents combined with immune checkpoint inhibitors) may disrupt this vicious cycle, offering novel avenues for enhancing therapeutic efficacy in HCC.

Multimodal Angiogenesis in HCC

The angiogenic cascade is a multistep process that is initiated by capillaries and effected by different types of specialized endothelial cells (ECs) and perivascular cells (PCs). These angiogenesis pathways are involved in the progression, invasion, and metastasis of tumors and drug resistance. Sprouting angiogenesis (SA) is a process in which new vessels bud from parental vesselsthat initiate in ECs and convert to tip cells in response to angiogenic signals. As migratory guiding cells, tip cells express matrix metalloproteases (MMPs), dissolve the extracellular matrix (ECM) and migrate along the VEGF gradient, and following tip cells are the trailing stalk cells, which elongate the vessels that sprout and branch from the existing vessels.[23,24] Next, lumen formation and expansion driven by VEGFA create new vascular networks, after which vascular smooth muscle cells (VSMCs) orPCs are recruited to support the new vasculature.[23,25] Endothelial sprouting primarily involves angiogenesis and is regulated by gene sets involved in proliferation, hypoxia, glycolysis and extracellular matrix formation, which are commonly upregulated in tumor ECs and include *Adamts 1, Angpt 2, Aplnr, Sparc* and many others.[26] In response to hypoxia, SA is promoted by HIF-1α and VEGF-induced delta-like protein 4 (Dll4) signaling in tip cells and Notch signaling in stalk cells (Dll4-Notch pathway).[27,28]

Vessel intussusception (VI) occurs when an existing vessel splits and separates into two vessels, which is a process that begins with intraluminal pillars via invagination of the vascular wall; these pillars may stretch across the vessel lumen with an intact basement membrane, resulting in vessel splitting. VIis activated in stable regions of the vascular network and is influenced by hypoxia, haemodynamic changes and shear stress.[29] The molecules involved in this process include MMT1-MMP, EphrinB2/EphB4-MAPK/ERK,[30] Notch-EphrinB2/EphB4[16] and SDF-1/CXCR4.[31] VI is not the major mechanism that occurs in cancer; however, VI can be stimulated after antiangiogenic therapy and can contribute to resistance to therapy.[32]

Vascular mimicry (VM) is an alternative mechanism by which cancer cells reposition themselves into structured vascular channels that are independent of ECs, which contributes to cancer progression and aggressiveness.[33] VM-proficient tumors account for the lack of response to sorafenib treatment in HCC patients[34] and challenge the classic

antiangiogenic treatment of HCC.[35] Inhibition of VM may increase sensitivity to sorafenib[36] and anti-PD-1 therapy.[37] The hypoxia angiogenesis cascade is crucial in VM,[34] as the activated HIF-1α/VEGFA signaling pathway promotes VM in HCC.[38] In addition, HIF-1 also regulates the expression of other epithelial transformation-related molecules, including Twist, LOX, and MMPs, and the Snail/FBP1/VEGF pathway in HCC, which promotes extracellular matrix remodelling and VM.[39] The Nrf2/ASPM axis drives VM in HCC under hypoxic conditions, which provides potential therapeutic targets for HCC.[40] Targeted VM therapy has become a focus for reversing resistance to antitumor therapy.

Vessel co-option (VCO) is a nonangiogenic mechanism in which cancer cells interact with and exploit preexisting vessels to obtain oxygen and nutrients rather than induce angiogenesis. Cancer cells migrate in normal tissues along the well-arranged vascular architecture,[41] resulting in continuous paracancerous tissue invasion, which becomes one of the main routes of portal venous invasion. VC is observed in 60% of HCCs and in nearly 75% of sorafenib-resistant HCC tissues and is widely seen in liver metastases after antiangiogenic therapy.[42] Since VC is independent of endothelial cell-mediated angiogenesis, HCCs in which VC has occurred exhibit a poor response to bevacizumab.[43] VCO and VM are implicated in both intrinsic and acquired resistance to antiangiogenic therapy in HCC.[41,44] Both VCO and VM are therefore legitimate targets of novel therapeutic strategies.

Stromal and Immune Cells Crosstalk in Promotion Angiogenesis

Cancer stem cells (CSCs) contribute directly to tumor-associated angiogenesis through their ability to differentiate into ECs and form capillary-like channels, as seen in VM, which is partly responsible for cancer treatment failure.[45] In HCC, tumor cells associated with VM-formed channels express the stem cell factors SOX2 and OCT4, which suggests a new mechanism by which CSCs mediate tumor VM.[46] CSCs transdifferentiate into cells of the endothelial lineage via the secretion of proangiogenic factors, including VEGF, PDGF, IL-8, CXCR4, SDF-1, and CXCL12[47] and the key pathways involve Sonic hedgehog, Notch, Hh, and the WNT/β-catenin cascade.[48] Hypoxia promotes the differentiation of CSCs into endothelial progenitor cells via the release of proangiogenic factors and exosomes. As CSCs ultimately become functional endothelial cells, the highly vascularized tumor microenvironment fuels CSCs via juxtacrine and paracrine mechanisms,[49] which culminates in a vicious cycle. CSC-derived vasculatures exhibit resistance to conventional antitumor drugs, and thus the incorporation of CSC angiogenic inhibitors into comprehensive antiangiogenic strategies is necessary.

Bone marrow-derived endothelial progenitor cells (BM-EPCs) are recruited into HCC via the circulation and are directly incorporated into the endothelium by differentiation into ECs.[50] BM-EPCs contribute to angiogenesis in both primary and metastatic tumors. BM-EPCs express proangiogenic markers such as VE-cadherin, VEGFR-1, VEGFR-2, and Tie-2[51] and the cell surface markers CD133 and CD34. VEFGR2 induces the differentiation of EPCs, and $CD133^+$ $CD34^+$ $VEGFR2^+$ cells are mostly recruited to HCC and concentrated in tumor microvessels.[52] Cancer cells release proangiogenic cytokines including VEGF, FGF, GM-CSF, and osteopontin into the circulation, which causes the marrow microenvironment to become highly proangiogenic.[53]

Tumor cells reprogramme immune cells via secretion of IL-10, TGF-β, and VEGF, thereby establishing a predominant pro-angiogenic immune microenvironment in advanced malignancies. Tregs facilitate angiogenesis through the suppression of type 1 T helper (TH1) cells effectoractivity, whichattenuating the release of angiostatic cytokines including TNFα, IFNγ.[54] CCL28 promote Treg cells accumulation and increased VEGF levels and increases tumor angiogenesis.[55] M2 tumor-associated macrophages (TAM) enhances HCC metastasis by promoting angiogenesis.[56] CCL18 produced by TAMs contributing to its pro-angiogenic effectsby activating ERK and Akt/GSK-3β/Snail signaling in ECs, CCL18+ TAM infiltration positively associated with microvascular density incancer samples.[57] Myeloid-derived suppressor cells (MDSCs) significantly promote tumor angiogenesis by secreting VEGF, IL-10, and MMP-9.[58] On the contrary, some cells play a role in inhibiting angiogenesis, such as tumour-infiltrating cytotoxic CD8+ T cells suppress angiogenesis through IFN-γ, which inhibiting the proliferation of ECs.[58] Immune cell driven angiogenesis has general characteristics of tumor blood vessels, including vascular structural disorder, leakage, poor perfusion, further exacerbating tumor hypoxia and acidosis, forming a vicious cycle of hypoxia and angiogenesis. Abnormal blood vessels are important physical barriers that hinder immune cell infiltration and effector function, and are also key factors leading to resistance to anti-tumor therapy.

Diverse vascularization mechanisms can coexist and collaboratively not only fuel HCC growth and metastasis but also establish a "cold" tumor characterized by an immunosuppressive milieu, which significantly impedes lymphocytes infiltration into tumor lesions and substantially impairs their antitumor effector functions. These dual roles underscore the rationale for targeting angiogenesis to simultaneously disrupt tumor progression and potentiate immunotherapy efficacy.

Angiogenesis-Immunity Axis: Mechanisms of Resistance and Immune Evasion

TME is a complex cellular ecosystem characterized by hypoxia, immune evasion and angiogenesis and is where tumor cells, fibroblasts, infiltrating and resident immune cells, cytokines, the extracellular matrix and the vasculature interact. The TME is organized by tumor cells, and since it is correlated with increased VEGF activity and T-cell dysfunction, the TME represents a safe niche to counteract the activation of the immune system,[59] which includes attenuation of CTLs and expansion of Tregs. Most cancer cells evolve in this chronic immunosuppressive necroinflamed environment, which is beneficial for HCC progression. Importantly, the shaping of the tumor vasculature supports immune remodelling. Angiogenesis-related genes regulate TME diversity and complexity in HCC patients, predict invasion and guide immunotherapy selection.[60] Numerous studies have shownthat the tumor vasculature is associated with an immunosuppressive microenvironment.[61,62] Disrupted vascular networks and high interstitial pressure are physical barriers for the migration of CTLs and therapeutic agents.[63,64] The tumor vasculature can also inhibit immune cell activity viahypoxia,[65] whereas hypoxic signalling-driven immunosuppression by Tregs and type-2 conventional dendritic cells (cDC2s)[66,67] can promote immune escape from natural killer cells through IL-10-STAT3 signalling, which is promoted by hypoxia-inducible gene 2.[68] In addition, the overexpression of angiogenic factors impairs the function of multiple immune cells (Figure 1).[69] Tumor vascular normalization can relieve immunosuppression and reprogram cells to exhibit an immunostimulatory phenotype.[70]

Vascular Structure Barriers Remodeling Lymphocytes Infiltration

Tumor vasculature imposes structural barriers to the infiltration of lymphocytes and to effective tumor control, and thus normalizing the vasculature can increase tissue perfusion and enhance T-cell transmigration, which can lead to

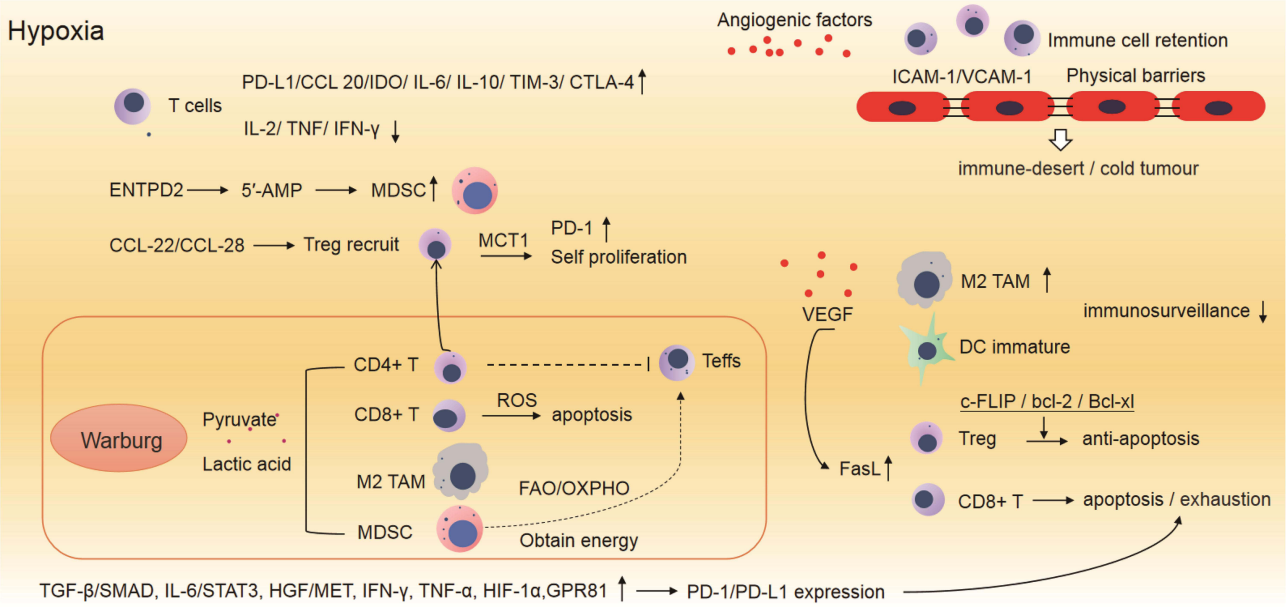

Figure 1 Angiogenic factors regulate the functioning of immune cells. Overexpression of angiogenic factors under hypoxic condition drives aberrant vasculature, which promotes immune cell retention and fosters an immune-desert tumor microenvironment. VEGF suppresses immune surveillance through multiple signaling pathways, induces M2 TAMs, impairs dendritic cell (DC) mature, expanding Tregs, and triggering $CD8^+$ T cell apoptosis. Hypoxia-induced upregulation of immune checkpoint molecules contributes significantly to immunosuppression. Warburg effect within the tumor microenvironment actively suppresses anti-tumor immunity via the accumulation of immunosuppressive metabolites, while simultaneously favoring the generation and function of immunosuppressive cell populations.

immunotherapy potentiation.[71–75] The infiltration of lymphocytes is a multistep process initiated by the interaction of lymphocytes with endothelial cells in high endothelial venules (HEVs).[76,77] Tumor-associated HEVs (TA-HEVs) exhibit an immature phenotype and specialize in naive and memory T-cell recruitment.[78] TA-HEVs are frequently found in areas rich in $CD3^+$T/$CD8^+$T or $CD20^+$Bcells.[79] The endothelium of HEVs expresses peripheral node addressin (PNAd), which serves as an L-selectin ligand andallows the selective recruitment of L-selectinhigh naive and memory T cells.[78] HEVs express high levels of MECA-79^+sulfatesialomucins and E/P-selectin, which are recognized by the lymphocyte homing receptor L-selectin (CD62L) and are associated with the homing of both naive and effector memory T cells to tumors.[80] Moreover, the integrin family, immunoglobulin gene superfamily, calcium-dependent cadherin family and other important molecules, such as CD44, that have not yet been classified are necessary for the extravasation of immune cells.

A key molecule that ensures EC barrier function is type II endothelium-specific cadherin and adhesion molecules on ECs are thought to be key activators of immune function.[81] Normalized levels and localization of VE-cadherin on ECs improve endothelial junction integrity and are critical for immune cell infiltration, which leads to increased invasion of $CD8^+$ T cells into tumors.[82] Immune cells in the peripheral blood come to rest on the endothelium by binding to chemokine-stimulated integrins.[83,84] Defective expression of integrin β3 is related to poor T-cell infiltration in HCC.[85] In addition, chemokine (C-X-C motif) ligands (CXCL) and CC-chemokine ligands (CCL) are expressed by ECs and bind to receptors expressed on $CD8^+$ T cells, which facilitates interactions between ECs and $CD8^+$T cells.[86] The abnormal expression of certain genes and epigenetic modifications can lead to excessive production of these chemokines, which promotes the growth and dispersion of tumor cells.

The tumor vasculature facilitates the infiltration of immunosuppressive cells and promotes an immunosuppressive phenotype.[87] Elevated IFP enhances the differential pressure of the transvascular transportation of T cells, and the low expression of VCAM-1 and ICAM-1 prevents the adhesion and transmigration of T cells.[88] Endothelial FasL is induced by tumor-derived VEGF-A, IL-10 and PGE2, which results in a decreased ratio of $CD8^+$ T cells to $FoxP3^+$ T cells.[89] Increased FasL expression in tumor endothelial cells selectively triggers the apoptosis of $CD8^+$ T cells instead of Tregs because of the expression of the antiapoptotic proteins c-FLIP, bcl-2 and Bcl-xl in Tregs.[90,91] Moreover, the absence of tumor-infiltrating lymphocytes (TILs) prevents antitumor immunity, which is typical of "cold" tumors that fail to respond to immunotherapy.[91] The SOD3/HIF-2α pathway shapes the tumor endothelium and allows it to be more permissive to adoptive cell transfer, and although endogenous tumor-specific $CD4^+$ and $CD8^+$ T cells depend on autocrine WNT pathway activation, the infiltration of myeloid and Treg cells is unaffected.[92,93] Activation of STING/IFN-I signaling induces normalization after a transient phase of vascular destruction, which facilitates the trafficking of effector T cells (Teffs) across the endothelial barrier and the regulation of the TME to enhance antitumor immunity.[94] Taken together, the TME limits the penetration of T cells from the vasculature and provides immune-privileged niches in which tumor cells can survive.

Hypoxia-Driven Signal Fuels Immune Suppression

Hypoxia is also clearly immunosuppressive, as it reduces the function of T cells and drives T-cell exhaustion via mitochondrial reprogramming.[95] Hypoxia alters how T cells respond to other signals, which increases the levels of immunosuppressive factors such as PD-L1,[22] CCL 20/IDO,[96] IL-6, IL-10, TIM-3 and CTLA-4.[97] Secretion of IL-2, TNF and IFN-γ is impaired in T cells under hypoxic conditions;[98] however, CTLA-4 expression is upregulated, increasing the sensitivity of TILs to negative regulation.[99,100] Hypoxia induces the expression of ENTPD2 in HCC, leading to elevated extracellular 5′-AMP, which promotes the maintenance of myeloid-derived suppressor cells (MDSCs).[101] CCL-22 and CCL-28 recruit Tregs into tumors[87,102,103] and attract $CCR6^+Foxp3^+$ Tregs through TREM-1^+ tumor-associated macrophages (TAMs) via the ERK/NF-κβ/CC20/CCR6 pathway.[104] The presence of Tregs results in a loss of antigen-presenting HLA-DR on cDC2s,[66] which modulates the immune response and angiogenesis and leads to effective immune escape. In addition, immunosuppressive myeloid subsets, such as M2 macrophages and cDC2s, were found to be significantly enriched in hypoxia-high tumor regions.[66]

Angiogenetic factors downstream of hypoxia drive immune suppression by directly inhibiting antigen-presenting cells (APCs) and Teffs and by enhancing the effects of Tregs, MDSCs and TAMs.[105] VEGF attenuates the expression of ICAM-1 and vascular adhesion moleculeon the vascular endothelium of tumors, which prevents immune cell infiltration.[106] VEGF stimulates the proliferation of Tregs, and blocking VEGFA/VEGFR-transduced signals counteracts

the induction of Tregs by tumor cells.[107,108] VEGF inhibits the maturation of DCs from precursors to enable tumor cells to escape immune surveillance[109,110] and induce the expansion of MDSCs.[111] VEGF significantly increases the expression of M2 markers on macrophages, and in one study, TAMs cultured in a VEGF-depleted environment presented lower levels of secreted cytokines involved in tumor progression and a decreased ability to induce immune tolerance.[112] VEGF also induces exhaustion of $CD8^+$ CTLs,[113] and blockade of VEGF synergistically modulates $CD8^+$ T-cell immune activity in tumors and potentiates their capacity to produce cytokines.[114]

Lactate Metabolism Fuels HCC Immunosuppression

The metabolism of HCC cells shifts from oxidative phosphorylation to anaerobic glycolysis under hypoxic conditions.[115,116] Metabolic rewiring of fatty acid and glucose metabolism across the stages of HCC has been identified.[117] Metabolic reprogramming and acidic metabolites prevent T-cell invasion and support the differentiation of $CD4^+$ T cells into Tregs rather than $CD4^+$Teffs.[118] In hypoxic settings, increased uptake of glucose by tumor cells leads to the loss of Teff metabolic activity and promotes the ageing phenotype,[100] and additionally, $CD8^+$ T cells accelerate differentiation to terminal exhaustion via metabolic byproducts, such as ROS, and repress effective antitumor immunity.[95] Antitumor immune cells typically display metabolic features that are complementary to those of their pretumor counterparts. Tregs, M2-TAMs, and MDSCs can utilize fatty acid oxidation (FAO) or oxidative phosphorylation (OXPHO) to provide cellular energy and maintain immune suppression against Teffs.[119,120] Loss of the metabolic regulator Sirt5 is associated with abnormally elevated bile acids, which promote M2-TAM polarization and favour an immunosuppressive TME.[121] Cell metabolism plays a central role in T-cell fate and suppresses antitumor immunity.

The reprogramming of energy metabolism and the Warburg effect in HCC result in the generation of pyruvate via glycolysis, which leads to the massive production of lactate.[122] Lactate acts as an immunosuppressive factor to promote tumor progression by inhibiting T-cell and NK cell functions or by supporting the functions of Tregs, TAMs, and MDSCs.[123] Tumor-derived lactate promotes pyruvate metabolism in $CD8^+$ T cells, which results in a loss of $CD8^+$ T-cell motility and cytotoxic function[124] and is an effect specific to $CD8^+$ T cells. $CD8^+$ CTLs can sense changes in the oxygen concentration through oxygen sensors and are highly sensitive to low pH and decreased cytotoxicity in a pH-dependent manner.[99] High levels of lactate or a low pH environment result in T-celland NK cell dysfunction, but Tregs are highly glycolytic and resistant to lactic acid. Tregs utilize lactic acid to feed the tricarboxylic acid (TCA) cycle and generate phosphoenolpyruvate to fuel self-proliferation in tumors, whereas the loss of lactate uptake by Tregs results in an environment conducive to immunotherapy.[123] Tregs actively absorb lactic acid through monocarboxylate transporter 1 (MCT1), which promotes NFAT1 translocation to increase the expression of PD-1.[125] Intratumoral lactate transport into macrophages is mediated by the mitochondrial pyruvate carrier (MPC), which promotes protumor macrophage activation[126] and blunts the antitumoral response of tumor-targeting T cells and NK cells.[127] In addition, lactate regulates PD-1 and PD-L1 expression through the TGF-β/SMAD, IL-6/STAT3, and HGF/MET signaling pathways and through cytokines and proteins such as IFN-γ, TNF-α, HIF-1α, and GPR81.[122] In summary, the acidic microenvironment and metabolites induced by hypoxia are antitumor reactions that are not conducive to tumor immunity.

Angiogenesis-Driven Immunosuppression: Crosstalk with PD-1/PD-L1 Axis

The spatial and functional heterogeneity of tumor vasculature perpetuates immunosuppression by dynamically modulating the PD-1/PD-L1 axis in hypoxia-adapted microenvironment. Mechanistically, hypoxia induces HIF-1α-dependent transcriptional upregulation of PD-L1 across MDSCs, M2-TAMs, DCs, and tumor cells.[128] Genetic or pharmacological inhibition of HIF-1α significantly reduces PD-L1 expression and synergizes with anti-PD-1 therapy to restore $CD8^+$ T cell cytotoxicity.[129] Intriguingly, PD-L1 blockade under hypoxic conditions not only enhances MDSC-mediated antigen presentation to T cells but also reprograms MDSC secretomes, suppressing immunosuppressive cytokines (IL-6, IL-10).[130] Emerging evidence reveals that immune checkpoint inhibitors reciprocally remodel vascular architecture. Anti-PD-1/PD-L1 therapies activate $CD4^+$ Th1 cells to secrete IFN-γ, which promotes endothelial normalization via increased pericyte coverage and reduced vascular leakage.[131] This "vascular normalization window" facilitates enhanced T cell infiltration and potentiates effector functions, establishing a feedforward loop between immune activation and hemodynamic improvement. In summary, immunotherapy and anti-angiogenic therapy engage in a bidirectional interplay, wherein immune checkpoint activation drives

vascular normalization, while remodeled vasculature enhances T cell trafficking and effector function, a self-reinforcing cycle that amplifies therapeutic efficacy. This vascular-immune crosstalk within TME mechanistically accounts for the suboptimal response rates (15–20%) to PD-1/PD-L1 inhibitor monotherapy while pinpointing critical targets for rational therapeutic combinations.

Current Strategies for Targeting Angiogenesis

In HCC, anti-angiogenic therapies synergize with PD-1 immunotherapy through multifaceted remodeling of the TME. By targeting pathological vascular networks driven by VEGF overproduction, these agents promote vascular normalization, which enhances Teffs infiltration while mitigating hypoxia-driven immunosuppression.[132,133] Vascular normalization reverses abnormal tumor vasculature's dual role in both physically excluding CTLs and fostering Treg recruitment.[134] Clinically, the combination of VEGF inhibitors with PD-1 blockade has shown superior objective response rates compared to monotherapy.[135] The success of the combination of atezolizumab and bevacizumab suggest that the TME was changed by bevacizumab, enabling greater responses to ICB therapy.[136] This dual targeting strategy overcomes angiogenesis-driven immune evasion, establishing a rationale for prioritizing combinatorial regimens in advanced HCC. Current challenges involve optimizing the "vascular normalization window" to balance perfusion improvement with excessive vessel pruning. Emerging strategies combine PD-1 inhibitors with multi-kinase anti-angiogenics to simultaneously target alternative pro-angiogenic pathways while reprogramming immunosuppressive niches. FDA approved anti-angiogenic drugs are shown in Supplementary Table 1, and the side effects of anti-angiogenic drugs and management are shown in Supplementary Table 2.

Antiangiogenic Therapy Synergy Advances HCC Treatment

An early theory was based on the blood and oxygen supply of the tumor vasculature and stated that the effect of starving tumors was achieved by blocking the tumor vasculature.[137] Single-agent bevacizumab treatment was shown to be associated with significant reductions in HCC enhancement by DCE-MRI and reductions in circulating VEGF-A and stromal-derived factor-1 levels and functional angiogenic activity.[138] Early antiangiogenic activity in HCC was evaluated via computed tomography perfusion (CTP) scans, which revealed a significant decrease in tumor blood flow, blood volume, and permeability surface area and an increase in the mean transit time.[139,140] Other methods for monitoring blood flow include dynamic US, which can quantify dynamic changes in vascularity as early as 3 days after bevacizumab therapy.[141] Antiangiogenic therapy is based mainly on the inhibition of VEGF, and most strategies used in the clinic combine anti-VEGF therapy with other therapies. As early as 2006, gemcitabine/oxaliplatin with bevacizumab was safely administered and has exhibited moderate antitumor activity for patients with advanced HCC.[142] In addition, the efficacy of bevacizumab combined with erlotinib[143] and capecitabine[144] has been validated in the clinic. In addition, several multitarget tyrosine kinase inhibitors, such as sorafenib, apatinib and lenvatinib, which exhibit antiangiogenic and antitumor effects, have been widely used in advanced HCC patients. Given the advancements in immunotherapy and its outstanding clinical efficacy, the combination of anti-angiogenesis therapy and immunotherapy has yielded significant results and has established itself as a first-line treatment for advanced HCC.

Vascular Normalization Optimizes HCC Therapeutic Outcomes

Although antiangiogenic agents have been used to treat tumors, extensive vascular pruning has demonstrated limited efficacy.[145] Hypoperfusion increases hypoxia, which promotes tumor invasion and metastasis by stimulating growth factor production.[146] Hypoxia enhances the stemness of HCC cells,[147,148] which is closely related to recurrence and drug resistance,[149,150] and a stemness–hypoxia–related prognostic signature has been developed to predict the efficacy of immunotherapy.[151] Optimizing the use of anti-VEGF agents induces vascular normalization, restores tumor perfusion and oxygenation, limits tumor cell invasiveness and improves the effectiveness of anticancer treatments.[152,153] Vascular normalization can be induced by targeting VEGF-VEGFR, Ang-Tie2, and PDGFR signaling in endothelial cells or oncogenic signaling in cancer cells.[145] Recombinant monoclonal antibodies and small-molecule TKIs are the primary drugs used to induce normalization and have improved oxygen delivery and blocked hypoxia-induced signaling pathways, thus alleviating

hypoxia and achieving combinatorial therapeutic benefits.[61,73,102] The optimal dose of lenvatinib that promotes vascular normalization via NRP-1-PDGFRβ has confirmed its enhanced synergistic effect with immunotherapy in HCC.[154]

The process of vascular normalization is closely related to the time window, the period during which the vasculature exhibits a normal phenotype and when antitumor agents might flow more easily into the tumor tissue through the circulation. The majority of normalization time windows following antiangiogenic treatment typically range from 2–4 days posttherapy. Accurate monitoring of the time window is beneficial for the accurate treatment of patients.[155] Although PET, MRI, ultrasound and CT perfusion imaging have been used to evaluate the efficacy of antiangiogenic therapy, MRI and ultrasound are the most commonly reported methods in the clinic. Blood oxygenation level-dependent MRI (BOLD-MRI) accurately monitors changes in oxygen content and can indirectly reflect changes in vascular function.[156] 18F-FMISO PET can monitor the interstitial oxygen state and help display the normalization time window.[157] Nevertheless, a consensus on the optimal imaging modality has yet to be established. Next, we will focus on the development of a set of clinical application guidelines for the evaluation of vascular normalization.

Combination Immunotherapy Transforms HCC Treatment Outcomes

The PD-1/PD-L1 axis mediates immune evasion in HCC by suppressing T-cell activation and promoting T-cell exhaustion. ICIs targeting the PD-1/PD-L1 axis reinvigorate exhausted T cells, revolutionized HCC management, yet only a subset of patients achieves durable responses. In the CheckMate 040 trial, the anti-PD-1 inhibitor nivolumab monotherapy demonstrated manageable safety, and the objective response rate was 20% in advanced HCC patients.[158] Emerging evidence suggests that the combination of ICIs with conventional or targeted therapies provides robust clinical benefits in patients and broadens the spectrum of patients who respond to ICIs (Figure 2). The ORR of patients treated with ramucirumab (anti-VEGFR2) plus durvalumab (anti-PD-L1) was 11%, the median progression-free survival was 4.4 months, and the overall survival was 10.7 months in patients with HCC, specifically in those with high PD-L1 expression.[159] Nivolumab–ipilimumab combination regimens elicit durable responses with high ORRs, and these responses occur regardless of HCC aetiology or PD-L1 expression,[160] which supports their use as a second-line treatment in HCC patients.[161] The regimen of single tremelimumab plus regular interval durvalumab is associated with an improvement in the global health status/quality of life (GHS/QoL) rate and symptom benefits in individuals with unresectable HCC.[162]

Nivolumab and pembrolizumab were approved in 2017 as second-line therapies for HCC. Atezolizumab + bevacizumab (Bev-Ate) significantly improved OS and PFS in patients with unresectable HCC who had not received prior systemic therapy.[163–165] Bev-Ate was established as a standard first-line systemic treatment for unresectable HCC in 2020. Perioperative camrelizumab plus apatinib as a neoadjuvant therapy exhibits promising efficacy and manageable

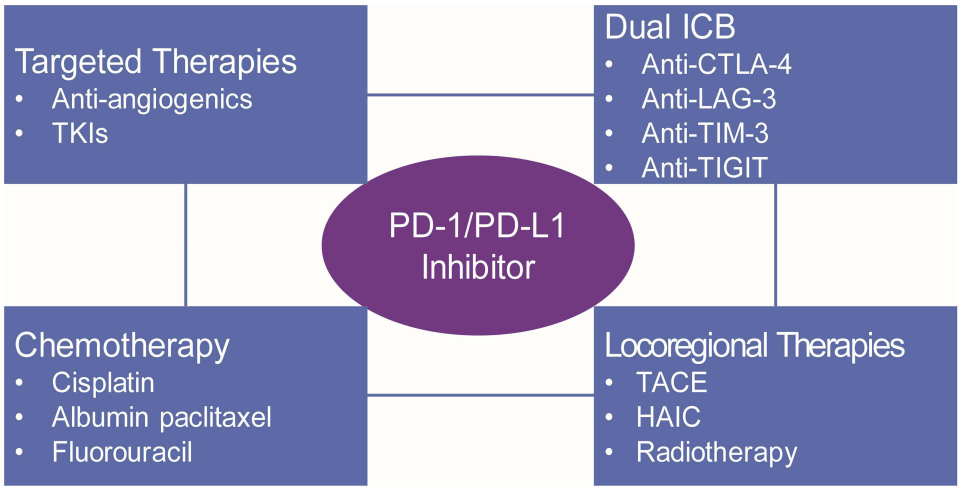

Figure 2 PD-1/PD-L1 inhibitors combined with other therapies. PD-1/PD-L1 inhibitors are primarily used in combination with targeted therapies (including anti-VEGF agents and tyrosine kinase inhibitors [TKIs]), another immune checkpoint inhibitor, conventional chemotherapy, or locoregional therapies (such as transarterial chemoembolization [TACE], hepatic arterial infusion chemotherapy [HAIC], and radiotherapy).

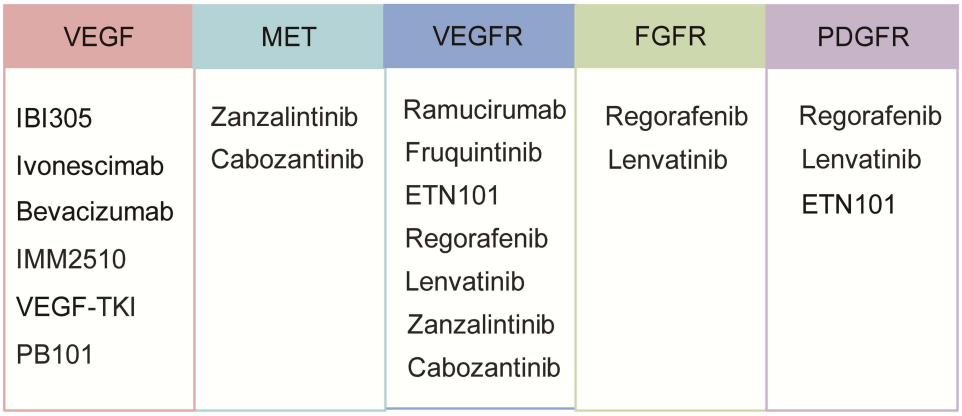

Figure 3 The main target of anti-angiogenesis therapy in clinical trials for HCC. VEGF/VEGFR represent the predominant therapeutic targets for inhibiting tumor angiogenesis. Furthermore, critical alternative targets encompass MET, FGFR, and PDGFR. Targeted agents inhibiting these pathways, including multi-kinase inhibitors, have entered the clinical armamentarium and represent a significant area of ongoing drug development.

toxicity in patients with resectable HCC.[166] The regimen consisting of lenvatinib plus anti-PD-1 antibodies is well tolerated and effective in converting unresectable HCC to resectable HCC.[167] GT90001 (an anti-ALK-1 monoclonal antibody) plus nivolumab is generally acceptable and manageable in patients with advanced HCC.[168] Sitravatinib (a spectrum-selective tyrosine kinase inhibitor) combined with tislelizumab is generally well tolerated and has shown preliminary antitumor activity in patients with unresectable, locally advanced, or metastatic HCC.[169] Combined therapy consisting of TQB2450 (an anti-PD-L1 antibody) and AL2846 (an antiangiogenic TKI) has a favourable safety profile in immunotherapy-refractory patients with advanced ESCC and HCC.[170] BMS-986,205 (an oral drug that selectively inhibits IDO) in combination with nivolumab as a first-line therapy in patients with advanced HCC has a manageable safety profile with durable benefits.[171] Sintilimab is also an effective adjuvant therapy for patients with HCC accompanied by microvascular invasion.[172]

In summary, the advent of immunotherapy has reshaped HCC treatment and undoubtedly offered new hope to patients with this disease. Although immunotherapy has achieved significant progress in the management of liver cancer, this therapeutic approach still faces numerous challenges. Ways to further enhance efficacy and reduce side effects, how to screen appropriate patient cohorts for immunotherapy, and how to optimize combination therapy strategies are all current research priorities. Additionally, with rapid advancements in technologies such as bioinformatics and artificial intelligence, personalized and precise immunotherapy will emerge as a future trend, providing patients with more efficient and safe treatment options. Anti-PD-1/PD-L1 maximizing its potential requires combinatorial strategies tailored to individual tumor biology.

Conclusion

The intimate interplay between tumor angiogenesis and immunosuppression has positioned combined angiogenesis inhibition and immunotherapy as a promising therapeutic strategy. Current clinical trials, as illustrated in Figure 3, predominantly target key angiogenic pathways, with most anti-angiogenic regimens now incorporating immunotherapy (detailed in Supplementary Table 3). While research in HCC targeting angiogenesis and immunity holds considerable potential, significant challenges persist. Vascular-targeted therapies confront intrinsic and acquired resistance to anti-angiogenic agents, activation of alternative pro-angiogenic pathways, and unresolved questions regarding the vascular normalization window—specifically its transient nature, optimal therapeutic timing, and monitoring difficulties. Immunotherapy with ICIs faces hurdles including limited response rates due to both innate and acquired resistance mechanisms, alongside the need for improved prediction and management of immune-related adverse events (irAEs). Combination strategies integrating vascular-targeted agents and ICIs confront dual challenges: identifying optimal synergistic regimens and elucidating their mechanistic foundations, coupled with the critical absence of validated predictive biomarkers for treatment efficacy. Addressing these challenges would substantially improve HCC patient prognosis and could offer broader translational insights for other solid tumors.

Funding

This work was supported by the Xiangshan Talent Foundation of Zhuhai People's Hospital (2022XSYC-02).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Gupta A, Seth R, Yadav A, Kurki V. Recent advances in ablative therapies for HCC. *J Clin Experiment Hepatol*. 2025;15(5):102592. doi:10.1016/j.jceh.2025.102592
2. Asafo-Agyei KO, Samant H. Hepatocellular carcinoma. In: *StatPearls*. Treasure Island (FL) ineligible companies; 2025.
3. Singh SP, Madke T, Chand P. Global epidemiology of hepatocellular carcinoma. *J Clin Experiment Hepatol*. 2025;15(2):102446. doi:10.1016/j.jceh.2024.102446
4. Koshy A. Evolving global Etiology of Hepatocellular Carcinoma (HCC): insights and trends for 2024. *J Clin Experiment Hepatol*. 2025;15(1):102406. doi:10.1016/j.jceh.2024.102406
5. Liu Y, Xun Z, Ma K, et al. Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. *J Hepatol*. 2023;78(4):770–782. doi:10.1016/j.jhep.2023.01.011
6. Moawad AW, Szklaruk J, Lall C, et al. Angiogenesis in hepatocellular carcinoma; pathophysiology, targeted therapy, and role of imaging. *J Hepatocell Carcinoma*. 2020;7:77–89. doi:10.2147/JHC.S224471
7. Jiang X, Xu Y, Chen D, et al. A novel angiogenesis-related prognostic signature associated with the hepatocellular carcinoma immune microenvironment and survival outcome. *Int J Gen Med*. 2022;15:311–323. doi:10.2147/IJGM.S349210
8. Cong Z, Zhao H, Zhang S, You T, Xie Y. LAGE3 promotes angiogenesis on hepatocellular carcinoma by stabilizing VEGFA mRNA. *Biochimica et biophysica acta*. 2024;1870(5):167196. doi:10.1016/j.bbadis.2024.167196
9. Lin JZ, Meng LL, Li YZ, et al. Importance of activated hepatic stellate cells and angiopoietin-1 in the pathogenesis of hepatocellular carcinoma. *Mol Med Rep*. 2016;14(2):1721–1725. doi:10.3892/mmr.2016.5418
10. Chen H, Nio K, Tang H, et al. BMP9-ID1 signaling activates HIF-1alpha and VEGFA expression to promote tumor angiogenesis in hepatocellular carcinoma. *Int J Mol Sci*. 2022;23(3):1475.
11. Han L, Lin X, Yan Q, et al. PBLD inhibits angiogenesis via impeding VEGF/VEGFR2-mediated microenvironmental cross-talk between HCC cells and endothelial cells. *Oncogene*. 2022;41(13):1851–1865. doi:10.1038/s41388-022-02197-x
12. Zhang F, Wang B, Zhang W, Xu Y, Zhang C, Xue X. Transcription factor MAZ potentiates the upregulated NEIL3-mediated aerobic glycolysis, thereby promoting angiogenesis in hepatocellular carcinoma. *Curr Cancer Drug Targets*. 2024;24(12):1235–1249. doi:10.2174/0115680096265896231226062212
13. Meng YM, Jiang X, Zhao X, et al. Hexokinase 2-driven glycolysis in pericytes activates their contractility leading to tumor blood vessel abnormalities. *Nat Commun*. 2021;12(1):6011. doi:10.1038/s41467-021-26259-y
14. Iwamoto H, Suzuki H, Masuda A, et al. A tumor endothelial cell-specific microRNA replacement therapy for hepatocellular carcinoma. *iScience*. 2024;27(2):108797. doi:10.1016/j.isci.2024.108797
15. Li W, Quan YY, Li Y, Lu L, Cui M. Monitoring of tumor vascular normalization: the key points from basic research to clinical application. *Cancer Manag Res*. 2018;10:4163–4172. doi:10.2147/CMAR.S174712
16. Zheng L, Yang C, Sheng R, et al. Characterization of microvascular invasion in hepatocellular carcinoma using computational modeling of interstitial fluid pressure and velocity. *J Magn Reson Imaging*. 2023;58(5):1366–1374. doi:10.1002/jmri.28644
17. Zhao Y, Ting KK, Coleman P, et al. The tumour vasculature as a target to modulate leucocyte trafficking. *Cancers*. 2021;13(7):1724. doi:10.3390/cancers13071724
18. Stylianopoulos T, Munn LL, Jain RK. Reengineering the tumor vasculature: improving drug delivery and efficacy. *Trend Cancer*. 2018;4(4):258–259. doi:10.1016/j.trecan.2018.02.010
19. Alfaro C, Suarez N, Gonzalez A, et al. Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes. *Br J Cancer*. 2009;100(7):1111–1119. doi:10.1038/sj.bjc.6604965
20. Wada J, Suzuki H, Fuchino R, et al. The contribution of vascular endothelial growth factor to the induction of regulatory T-cells in malignant effusions. *Anticancer Res*. 2009;29(3):881–888.
21. Lu X, Li L, Lin J, et al. PAARH promotes M2 macrophage polarization and immune evasion of liver cancer cells through VEGF protein. *Int J Biol Macromol*. 2024;281(Pt 4):136580. doi:10.1016/j.ijbiomac.2024.136580
22. Chen ZQ, Zuo XL, Cai J, et al. Hypoxia-associated circPRDM4 promotes immune escape via HIF-1alpha regulation of PD-L1 in hepatocellular carcinoma. *Experiment Hematol Oncol*. 2023;12(1):17. doi:10.1186/s40164-023-00378-2
23. Vakhrushev IV, Nezhurina EK, Karalkin PA, et al. Heterotypic multicellular spheroids as experimental and preclinical models of sprouting angiogenesis. *Biology*. 2021;11(1):18. doi:10.3390/biology11010018
24. Pulkkinen HH, Kiema M, Lappalainen JP, et al. BMP6/TAZ-hippo signaling modulates angiogenesis and endothelial cell response to VEGF. *Angiogenesis*. 2021;24(1):129–144. doi:10.1007/s10456-020-09748-4
25. Li G, Gao J, Ding P, Gao Y. The role of endothelial cell-pericyte interactions in vascularization and diseases. *J Adv Res*. 2024;67:269–88.
26. Rohlenova K, Goveia J, Garcia-Caballero M, et al. Single-cell RNA sequencing maps endothelial metabolic plasticity in pathological angiogenesis. *Cell Metab*. 2020;31(4):862–877e814. doi:10.1016/j.cmet.2020.03.009
27. Cha S, Kim HG, Jang H, et al. Steppogenin suppresses tumor growth and sprouting angiogenesis through inhibition of HIF-1alpha in tumors and DLL4 activity in the endothelium. *Phytomedicine*. 2023;108:154513. doi:10.1016/j.phymed.2022.154513

28. Oliveira RHM, Annex BH, Popel AS. Endothelial cells signaling and patterning under hypoxia: a mechanistic integrative computational model including the Notch-Dll4 pathway. *Front Physiol*. 2024;15:1351753. doi:10.3389/fphys.2024.1351753
29. Diaz-Flores L, Gutierrez R, Gonzalez-Gomez M, et al. Phenomena of intussusceptive angiogenesis and intussusceptive lymphangiogenesis in blood and lymphatic vessel tumors. *Biomedicines*. 2024;12(2). doi:10.3390/biomedicines12020258
30. Groppa E, Brkic S, Uccelli A, et al. EphrinB2/EphB4 signaling regulates non-sprouting angiogenesis by VEGF. *EMBO Rep*. 2018;19(5). doi:10.15252/embr.201745054
31. Dimova I, Karthik S, Makanya A, et al. SDF-1/CXCR4 signalling is involved in blood vessel growth and remodelling by intussusception. *J Cell Mol Med*. 2019;23(6):3916–3926. doi:10.1111/jcmm.14269
32. D'Amico G, Munoz-Felix JM, Pedrosa AR, Hodivala-Dilke KM. "Splitting the matrix": intussusceptive angiogenesis meets MT1-MMP. *EMBO Mol Med*. 2020;12(2):e11663. doi:10.15252/emmm.201911663
33. Xiao T, Bao J, Tian J, et al. Flavokawain A suppresses the vasculogenic mimicry of HCC by inhibiting CXCL12 mediated EMT. *Phytomedicine*. 2023;112:154687. doi:10.1016/j.phymed.2023.154687
34. Shi Y, Shang J, Li Y, et al. ITGA5 and ITGB1 contribute to Sorafenib resistance by promoting vasculogenic mimicry formation in hepatocellular carcinoma. *Cancer Med*. 2023;12(3):3786–3796. doi:10.1002/cam4.5110
35. Cannell IG, Sawicka K, Pearsall I, et al. FOXC2 promotes vasculogenic mimicry and resistance to anti-angiogenic therapy. *Cell Rep*. 2023;42 (8):112791. doi:10.1016/j.celrep.2023.112791
36. Zhang X, Zhang JG, Mu W, Zhou HM, Liu GL, Li Q. The role of daurisoline treatment in hepatocellular carcinoma: inhibiting vasculogenic mimicry formation and enhancing sensitivity to sorafenib. *Phytomedicine*. 2021;92:153740. doi:10.1016/j.phymed.2021.153740
37. Qin LN, Zhang H, Li QQ, et al. Vitamin D binding protein (VDBP) hijacks twist1 to inhibit vasculogenic mimicry in hepatocellular carcinoma. *Theranostics*. 2024;14(1):436–450. doi:10.7150/thno.90322
38. Fang T, Lin L, Ye ZJ, et al. Dexmedetomidine promotes angiogenesis and vasculogenic mimicry in human hepatocellular carcinoma through alpha (2)-AR/HIF-1alpha/VEGFA pathway. *Biomed Environ Sci*. 2022;35(10):931–942. doi:10.3967/bes2022.120
39. Fan Z, Zheng W, Li H, et al. LOXL2 upregulates hypoxia-inducible factor-1alpha signaling through Snail-FBP1 axis in hepatocellular carcinoma cells. *Oncol Rep*. 2020;43(5):1641–1649. doi:10.3892/or.2020.7541
40. Zhang Y, Che N, Wang S, et al. Nrf2/ASPM axis regulated vasculogenic mimicry formation in hepatocellular carcinoma under hypoxia. *J Gastroenterol*. 2024;59(10):941–957. doi:10.1007/s00535-024-02140-9
41. Ribatti D, Annese T, Tamma R. Vascular co-option in resistance to anti-angiogenic therapy. *Front Oncol*. 2023;13:1323350. doi:10.3389/fonc.2023.1323350
42. Yang D, Dang S, Wang Z, Xie M, Li X, Ding X. Vessel co-option: a unique vascular-immune niche in liver cancer. *Front Oncol*. 2024;14:1386772. doi:10.3389/fonc.2024.1386772
43. Lazaris A, Amri A, Petrillo SK, et al. Vascularization of colorectal carcinoma liver metastasis: insight into stratification of patients for anti-angiogenic therapies. *J Pathol*. 2018;4(3):184–192. doi:10.1002/cjp2.100
44. Kuczynski EA, Yin M, Bar-Zion A, et al. Co-option of liver vessels and not sprouting angiogenesis drives acquired sorafenib resistance in hepatocellular carcinoma. *J Natl Cancer Inst*. 2016;108(8):djw030. doi:10.1093/jnci/djw030
45. Li F, Xu J, Liu S. Cancer stem cells and neovascularization. *Cells*. 2021;10(5):1070.
46. Zhao X, Sun B, Sun D, et al. Slug promotes hepatocellular cancer cell progression by increasing sox2 and nanog expression. *Oncol Rep*. 2015;33(1):149–156. doi:10.3892/or.2014.3562
47. Yang Y, Guo J, Li M, et al. Cancer stem cells and angiogenesis. *Pathol Res Pract*. 2024;253:155064. doi:10.1016/j.prp.2023.155064
48. Yadav AK, Desai NS. Cancer stem cells: acquisition, characteristics, therapeutic implications, targeting strategies and future prospects. *Stem Cell Rev Rep*. 2019;15(3):331–355. doi:10.1007/s12015-019-09887-2
49. Yao H, Liu N, Lin MC, Zheng J. Positive feedback loop between cancer stem cells and angiogenesis in hepatocellular carcinoma. *Cancer Lett*. 2016;379(2):213–219. doi:10.1016/j.canlet.2016.03.014
50. Zhu H, Shao Q, Sun X, et al. The mobilization, recruitment and contribution of bone marrow-derived endothelial progenitor cells to the tumor neovascularization occur at an early stage and throughout the entire process of hepatocellular carcinoma growth. *Oncol Rep*. 2012;28 (4):1217–1224. doi:10.3892/or.2012.1944
51. Shaked Y, Voest EE. Bone marrow derived cells in tumor angiogenesis and growth: are they the good, the bad or the evil? *Biochimica et biophysica acta*. 2009;1796(1):1–4. doi:10.1016/j.bbcan.2009.07.002
52. Sun XT, Yuan XW, Zhu HT, et al. Endothelial precursor cells promote angiogenesis in hepatocellular carcinoma. *World J Gastroenterol*. 2012;18(35):4925–4933. doi:10.3748/wjg.v18.i35.4925
53. Gao D, Nolan D, McDonnell K, et al. Bone marrow-derived endothelial progenitor cells contribute to the angiogenic switch in tumor growth and metastatic progression. *Biochimica et biophysica acta*. 2009;1796(1):33–40. doi:10.1016/j.bbcan.2009.05.001
54. Muller-Hermelink N, Braumuller H, Pichler B, et al. TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multistage carcinogenesis. *Cancer cell*. 2008;13(6):507–518.
55. Motz GT, Coukos G. The parallel lives of angiogenesis and immunosuppression: cancer and other tales. *Nat Rev Immunol*. 2011;11 (10):702–711. doi:10.1038/nri3064
56. Lu Y, Han G, Zhang Y, et al. M2 macrophage-secreted exosomes promote metastasis and increase vascular permeability in hepatocellular carcinoma. *Cell Commun signal*. 2023;21(1):299. doi:10.1186/s12964-022-00872-w
57. Lin L, Chen YS, Yao YD, et al. CCL18 from tumor-associated macrophages promotes angiogenesis in breast cancer. *Oncotarget*. 2015;6 (33):34758–34773. doi:10.18632/oncotarget.5325
58. Kim HJ, Ji YR, Lee YM. Crosstalk between angiogenesis and immune regulation in the tumor microenvironment. *Arch Pharm Res*. 2022;45 (6):401–416.
59. Chen S, Liao C, Hu H, et al. Hypoxia-driven tumor stromal remodeling and immunosuppressive microenvironment in scirrhous HCC. *Hepatology*. 2024;79(4):780–797. doi:10.1097/HEP.0000000000000599
60. Li W, Wu R, Zhang S, et al. Analysis of angiogenesis-related subtypes of hepatocellular carcinoma and tumor microenvironment infiltration feature in hepatocellular carcinoma. *Clin Trans Oncol*. 2023;25(7):2099–2115. doi:10.1007/s12094-023-03084-x

61. He Y, Zhan L, Shi J, et al. The combination of R848 with sorafenib enhances antitumor effects by reprogramming the tumor immune microenvironment and facilitating vascular normalization in hepatocellular carcinoma. *Adv Sci*. 2023;10(18):e2207650. doi:10.1002/advs.202207650
62. Kuo CL, Chou HY, Lien HW, et al. A Fc-VEGF chimeric fusion enhances PD-L1 immunotherapy via inducing immune reprogramming and infiltration in the immunosuppressive tumor microenvironment. *Cancer Immunol Immunother*. 2023;72(2):351–369. doi:10.1007/s00262-022-03255-9
63. Jain RK. Vascular and interstitial barriers to delivery of therapeutic agents in tumors. *Cancer Metastasis Rev*. 1990;9(3):253–266. doi:10.1007/BF00046364
64. Chen SC, Wu PC, Wang CY, Kuo PL. Evaluation of cytotoxic T lymphocyte-mediated anticancer response against tumor interstitium-simulating physical barriers. *Sci Rep*. 2020;10(1):13662. doi:10.1038/s41598-020-70694-8
65. Lee HH, Kang H, Cho H. Role of Interleukin(IL)-6 in NK activity to hypoxic-induced highly invasive Hepatocellular Carcinoma(HCC) Cells. *J Microbiol Biotechnol*. 2023;33(7):864–874. doi:10.4014/jmb.2304.04023
66. Suthen S, Lim CJ, Nguyen PHD, et al. Hypoxia-driven immunosuppression by Treg and type-2 conventional dendritic cells in HCC. *Hepatology*. 2022;76(5):1329–1344. doi:10.1002/hep.32419
67. Jayaprakash P, Vignali PDA, Delgoffe GM, Curran MA. Hypoxia reduction sensitizes refractory cancers to immunotherapy. *Ann Rev Med*. 2022;73:251–265. doi:10.1146/annurev-med-060619-022830
68. Cui C, Fu K, Yang L, et al. Hypoxia-inducible gene 2 promotes the immune escape of hepatocellular carcinoma from nature killer cells through the interleukin-10-STAT3 signaling pathway. *J Exp Clin Cancer Res*. 2019;38(1):229. doi:10.1186/s13046-019-1233-9
69. Qi Y, Song Y, Cai M, et al. Vascular endothelial growth factor A is a potential prognostic biomarker and correlates with immune cell infiltration in hepatocellular carcinoma. *J Cell Mol Med*. 2023;27(4):538–552. doi:10.1111/jcmm.17678
70. Mao D, Wang H, Guo H, et al. Tanshinone IIA normalized hepatocellular carcinoma vessels and enhanced PD-1 inhibitor efficacy by inhibiting ELTD1. *Phytomedicine*. 2024;123:155191. doi:10.1016/j.phymed.2023.155191
71. Wang-Bishop L, Kimmel BR, Ngwa VM, et al. STING-activating nanoparticles normalize the vascular-immune interface to potentiate cancer immunotherapy. *Sci Immunol*. 2023;8(83):eadd1153. doi:10.1126/sciimmunol.add1153
72. Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL, Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. *Nat Rev Immunol*. 2018;18(3):195–203. doi:10.1038/nri.2017.145
73. Han Y, Pan Q, Guo Z, et al. BMP9-induced vascular normalisation improves the efficacy of immunotherapy against hepatitis B virus-associated hepatocellular carcinoma. *Clin Trans Med*. 2023;13(5):e1247. doi:10.1002/ctm2.1247
74. Shigeta K, Datta M, Hato T, et al. Dual programmed death receptor-1 and vascular endothelial growth factor receptor-2 blockade promotes vascular normalization and enhances antitumor immune responses in hepatocellular carcinoma. *Hepatology*. 2020;71(4):1247–1261. doi:10.1002/hep.30889
75. Shigeta K, Matsui A, Kikuchi H, et al. Regorafenib combined with PD1 blockade increases CD8 T-cell infiltration by inducing CXCL10 expression in hepatocellular carcinoma. *J Immunother Cancer*. 2020;8(2):e001435. doi:10.1136/jitc-2020-001435
76. Song J, Zhang X, Buscher K, et al. Endothelial basement membrane laminin 511 contributes to endothelial junctional tightness and thereby inhibits leukocyte transmigration. *Cell Rep*. 2017;18(5):1256–1269. doi:10.1016/j.celrep.2016.12.092
77. Umemoto E, Hayasaka H, Bai Z, et al. Novel regulators of lymphocyte trafficking across high endothelial venules. *Crit Rev Immunol*. 2011;31(2):147–169. doi:10.1615/CritRevImmunol.v31.i2.40
78. Sawada J, Perrot CY, Chen L, et al. High endothelial venules accelerate naive T cell recruitment by tumor necrosis factor-mediated r-ras upregulation. *Am J Pathol*. 2021;191(2):396–414. doi:10.1016/j.ajpath.2020.10.009
79. Blanchard L, Girard JP. High endothelial venules (HEVs) in immunity, inflammation and cancer. *Angiogenesis*. 2021;24(4):719–753. doi:10.1007/s10456-021-09792-8
80. Asrir A, Tardiveau C, Coudert J, et al. Tumor-associated high endothelial venules mediate lymphocyte entry into tumors and predict response to PD-1 plus CTLA-4 combination immunotherapy. *Cancer Cell*. 2022;40(3):318–334e319. doi:10.1016/j.ccell.2022.01.002
81. Dustin ML. Role of adhesion molecules in activation signaling in T lymphocytes. *J Clin Immunol*. 2001;21(4):258–263. doi:10.1023/A:1010927208180
82. Zhao Y, Li J, Ting KK, et al. The VE-Cadherin/beta-catenin signalling axis regulates immune cell infiltration into tumours. *Cancer Lett*. 2021;496:1–15. doi:10.1016/j.canlet.2020.09.026
83. Shulman Z, Shinder V, Klein E, et al. Lymphocyte crawling and transendothelial migration require chemokine triggering of high-affinity LFA-1 integrin. *Immunity*. 2009;30(3):384–396. doi:10.1016/j.immuni.2008.12.020
84. Estin ML, Thompson SB, Traxinger B, Fisher MH, Friedman RS, Jacobelli J. Ena/VASP proteins regulate activated T-cell trafficking by promoting diapedesis during transendothelial migration. *Proc Natl Acad Sci U S A* 2017;114(14):E2901–E2910. doi:10.1073/pnas.1701886114
85. Zhou M, Feng Y, Zhang X, et al. Platelet-derived microparticles adoptively transfer integrin beta3 to promote antitumor effect of tumor-infiltrating T cells. *Oncoimmunology*. 2024;13(1):2304963. doi:10.1080/2162402X.2024.2304963
86. Korbecki J, Grochans S, Gutowska I, Barczak K, Baranowska-Bosiacka I. CC chemokines in a tumor: a review of pro-cancer and anti-cancer properties of receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 ligands. *Int J Mol Sci*. 2020;21(20):8412.
87. Zheng W, Qian C, Tang Y, et al. Manipulation of the crosstalk between tumor angiogenesis and immunosuppression in the tumor microenvironment: insight into the combination therapy of anti-angiogenesis and immune checkpoint blockade. *Front Immunol*. 2022;13:1035323. doi:10.3389/fimmu.2022.1035323
88. Yoong KF, McNab G, Hubscher SG, Adams DH. Vascular adhesion protein-1 and ICAM-1 support the adhesion of tumor-infiltrating lymphocytes to tumor endothelium in human hepatocellular carcinoma. *J Immunol*. 1998;160(8):3978–3988. doi:10.4049/jimmunol.160.8.3978
89. Motz GT, Santoro SP, Wang LP, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat Med*. 2014;20(6):607–615. doi:10.1038/nm.3541
90. Cai Y, Zhu B, Shan X, et al. Inhibiting endothelial cell-mediated t lymphocyte apoptosis with integrin-targeting peptide-drug conjugate filaments for chemoimmunotherapy of triple-negative breast cancer. *Adv Mater*. 2024;36(3):e2306676. doi:10.1002/adma.202306676
91. Zhu J, Petit PF, Van den Eynde BJ. Apoptosis of tumor-infiltrating T lymphocytes: a new immune checkpoint mechanism. *Cancer Immunol Immunother*. 2019;68(5):835–847. doi:10.1007/s00262-018-2269-y
92. Martinez-Rey D, Carmona-Rodriguez L, Fernandez-Acenero MJ, Mira E, Manes S. Extracellular superoxide dismutase, the endothelial basement membrane, and the WNT pathway: new players in vascular normalization and tumor infiltration by T-cells. *Front Immunol*. 2020;11:579552. doi:10.3389/fimmu.2020.579552

93. Carmona-Rodriguez L, Martinez-Rey D, Fernandez-Acenero MJ, et al. SOD3 induces a HIF-2alpha-dependent program in endothelial cells that provides a selective signal for tumor infiltration by T cells. *J Immunother Cancer*. 2020;8(1):e000432. doi:10.1136/jitc-2019-000432
94. Yang H, Lee WS, Kong SJ, et al. STING activation reprograms tumor vasculatures and synergizes with VEGFR2 blockade. *J Clin Invest*. 2019;129(10):4350–4364. doi:10.1172/JCI125413
95. Scharping NE, Rivadeneira DB, Menk AV, et al. Mitochondrial stress induced by continuous stimulation under hypoxia rapidly drives T cell exhaustion. *Nat Immunol*. 2021;22(2):205–215. doi:10.1038/s41590-020-00834-9
96. Ye LY, Chen W, Bai XL, et al. Hypoxia-induced epithelial-to-mesenchymal transition in hepatocellular carcinoma induces an immunosuppressive tumor microenvironment to promote metastasis. *Cancer Res*. 2016;76(4):818–830. doi:10.1158/0008-5472.CAN-15-0977
97. Davern M, Donlon NE, O'Connell F, et al. Nutrient deprivation and hypoxia alter T cell immune checkpoint expression: potential impact for immunotherapy. *J Cancer Res Clin Oncol*. 2023;149(8):5377–5395. doi:10.1007/s00432-022-04440-0
98. Blagih J, Coulombe F, Vincent EE, et al. The energy sensor AMPK regulates T cell metabolic adaptation and effector responses in vivo. *Immunity*. 2015;42(1):41–54. doi:10.1016/j.immuni.2014.12.030
99. Li Y, Patel SP, Roszik J, Qin Y. Hypoxia-driven immunosuppressive metabolites in the tumor microenvironment: new approaches for combinational immunotherapy. *Front Immunol*. 2018;9:1591. doi:10.3389/fimmu.2018.01591
100. Leone RD, Powell JD. Metabolism of immune cells in cancer. *Nat Rev Cancer*. 2020;20(9):516–531. doi:10.1038/s41568-020-0273-y
101. Chiu DK, Tse AP, Xu IM, et al. Hypoxia inducible factor HIF-1 promotes myeloid-derived suppressor cells accumulation through ENTPD2/CD39L1 in hepatocellular carcinoma. *Nat Commun*. 2017;8(1):517. doi:10.1038/s41467-017-00530-7
102. Fan P, Zhang N, Candi E, et al. Alleviating hypoxia to improve cancer immunotherapy. *Oncogene*. 2023;42(49):3591–3604. doi:10.1038/s41388-023-02869-2
103. Ren L, Yu Y, Wang L, Zhu Z, Lu R, Yao Z. Hypoxia-induced CCL28 promotes recruitment of regulatory T cells and tumor growth in liver cancer. *Oncotarget*. 2016;7(46):75763–75773. doi:10.18632/oncotarget.12409
104. Wu Q, Zhou W, Yin S, et al. Blocking triggering receptor expressed on myeloid cells-1-positive tumor-associated macrophages induced by hypoxia reverses immunosuppression and anti-programmed cell death ligand 1 resistance in liver cancer. *Hepatology*. 2019;70(1):198–214. doi:10.1002/hep.30593
105. Rahma OE, Hodi FS. The intersection between tumor angiogenesis and immune suppression. *Clin Cancer Res*. 2019;25(18):5449–5457. doi:10.1158/1078-0432.CCR-18-1543
106. Munn LL, Jain RK. Vascular regulation of antitumor immunity. *Science*. 2019;365(6453):544–545. doi:10.1126/science.aaw7875
107. Terme M, Tartour E, Taieb J. VEGFA/VEGFR2-targeted therapies prevent the VEGFA-induced proliferation of regulatory T cells in cancer. *Oncoimmunology*. 2013;2(8):e25156. doi:10.4161/onci.25156
108. Terme M, Pernot S, Marcheteau E, et al. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res*. 2013;73(2):539–549. doi:10.1158/0008-5472.CAN-12-2325
109. Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Sig Transduct Targeted Ther*. 2023;8(1):198. doi:10.1038/s41392-023-01460-1
110. Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med*. 1996;2(10):1096–1103. doi:10.1038/nm1096-1096
111. Tian Y, Gao X, Yang X, Chen S, Ren Y. VEGFA contributes to tumor property of glioblastoma cells by promoting differentiation of myeloid-derived suppressor cells. *BMC Cancer*. 2024;24(1):1040. doi:10.1186/s12885-024-12803-8
112. Okikawa S, Morine Y, Saito Y, et al. Inhibition of the VEGF signaling pathway attenuates tumor-associated macrophage activity in liver cancer. *Oncol Rep*. 2022;47(4). doi:10.3892/or.2022.8282
113. Kim CG, Jang M, Kim Y, et al. VEGF-A drives TOX-dependent T cell exhaustion in anti-PD-1-resistant microsatellite stable colorectal cancers. *Sci Immunol*. 2019;4(41). doi:10.1126/sciimmunol.aay0555
114. de Almeida PE, Mak J, Hernandez G, et al. Anti-VEGF treatment enhances CD8(+) T-cell antitumor activity by amplifying hypoxia. *Cancer Immunol Res*. 2020;8(6):806–818. doi:10.1158/2326-6066.CIR-19-0360
115. Zhao F, Yu W, Hu J, et al. Hypoxia-induced TRPM7 promotes glycolytic metabolism and progression in hepatocellular carcinoma. *Eur J Pharmacol*. 2024;974:176601. doi:10.1016/j.ejphar.2024.176601
116. Zhang H, Su X, Burley SK, Zheng XFS. mTOR regulates aerobic glycolysis through NEAT1 and nuclear paraspeckle-mediated mechanism in hepatocellular carcinoma. *Theranostics*. 2022;12(7):3518–3533. doi:10.7150/thno.72581
117. Balakrishnan K. Hepatocellular carcinoma stage: an almost loss of fatty acid metabolism and gain of glucose metabolic pathways dysregulation. *Med Oncol*. 2022;39(12):247. doi:10.1007/s12032-022-01839-0
118. Lian X, Yang K, Li R, et al. Immunometabolic rewiring in tumorigenesis and anti-tumor immunotherapy. *Mol Cancer*. 2022;21(1):27. doi:10.1186/s12943-021-01486-5
119. Bader JE, Voss K, Rathmell JC. Targeting metabolism to improve the tumor microenvironment for cancer immunotherapy. *Mol Cell*. 2020;78(6):1019–1033. doi:10.1016/j.molcel.2020.05.034
120. Lin J, Rao D, Zhang M, Gao Q. Metabolic reprogramming in the tumor microenvironment of liver cancer. *J Hematol Oncol*. 2024;17(1):6. doi:10.1186/s13045-024-01527-8
121. Sun R, Zhang Z, Bao R, et al. Loss of SIRT5 promotes bile acid-induced immunosuppressive microenvironment and hepatocarcinogenesis. *J Hepatol*. 2022;77(2):453–466. doi:10.1016/j.jhep.2022.02.030
122. Xu Y, Hao X, Ren Y, et al. Research progress of abnormal lactate metabolism and lactate modification in immunotherapy of hepatocellular carcinoma. *Front Oncol*. 2022;12:1063423. doi:10.3389/fonc.2022.1063423
123. Watson MJ, Vignali PDA, Mullett SJ, et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature*. 2021;591(7851):645–651.
124. Elia I, Rowe JH, Johnson S, et al. Tumor cells dictate anti-tumor immune responses by altering pyruvate utilization and succinate signaling in CD8(+) T cells. *Cell Metab*. 2022;34(8):1137–1150e1136. doi:10.1016/j.cmet.2022.06.008
125. Kumagai S, Koyama S, Itahashi K, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell*. 2022;40(2):201–218e209. doi:10.1016/j.ccell.2022.01.001

126. Fang X, Zhao P, Gao S, et al. Lactate induces tumor-associated macrophage polarization independent of mitochondrial pyruvate carrier-mediated metabolism. *Int J Biol Macromol*. 2023;237:123810. doi:10.1016/j.ijbiomac.2023.123810
127. Brand A, Singer K, Koehl GE, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab*. 2016;24(5):657–671. doi:10.1016/j.cmet.2016.08.011
128. Bigos KJ, Quiles CG, Lunj S, et al. Tumour response to hypoxia: understanding the hypoxic tumour microenvironment to improve treatment outcome in solid tumours. *Front Oncol*. 2024;14:1331355. doi:10.3389/fonc.2024.1331355
129. Ding XC, Wang LL, Zhang XD, et al. The relationship between expression of PD-L1 and HIF-1alpha in glioma cells under hypoxia. *J Hematol Oncol*. 2021;14(1):92. doi:10.1186/s13045-021-01102-5
130. Noman MZ, Desantis G, Janji B, et al. PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Experimet Med*. 2014;211(5):781–790. doi:10.1084/jem.20131916
131. Tian L, Goldstein A, Wang H, et al. Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. *Nature*. 2017;544(7649):250–254. doi:10.1038/nature21724
132. Zhang D, Jiang C, Zheng X, et al. Normalization of tumor vessels by lenvatinib-based metallo-nanodrugs alleviates hypoxia and enhances calreticulin-mediated immune responses in orthotopic HCC and organoids. *Small*. 2023;19(29):e2207786. doi:10.1002/smll.202207786
133. Liu J, Bai Y, Liu X, et al. Enhanced efficacy of combined VEGFR peptide-drug conjugate and anti-PD-1 antibody in treating hepatocellular carcinoma. *Sci Rep*. 2024;14(1):21728. doi:10.1038/s41598-024-72907-w
134. Wei F, Su Y, Quan Y, et al. Anticoagulants enhance molecular and cellular immunotherapy of cancer by improving tumor microcirculation structure and function and redistributing tumor infiltrates. *Clin Cancer Res*. 2023;29(13):2525–2539. doi:10.1158/1078-0432.CCR-22-2757
135. Kudo M, Finn RS, Galle PR, et al. IMbrave150: efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in patients with barcelona clinic liver cancer stage B unresectable hepatocellular carcinoma: an exploratory analysis of the phase III study. *Liver Cancer*. 2023;12(3):238–250. doi:10.1159/000528272
136. Cappuyns S, Philips G, Vandecaveye V, et al. PD-1(-) CD45RA(+) effector-memory CD8 T cells and CXCL10(+) macrophages are associated with response to atezolizumab plus bevacizumab in advanced hepatocellular carcinoma. *Nat Commun*. 2023;14(1):7825. doi:10.1038/s41467-023-43381-1
137. Folkman J. Anti-angiogenesis: new concept for therapy of solid tumors. *Ann Surg*. 1972;175(3):409–416. doi:10.1097/00000658-197203000-00014
138. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol*. 2008;26(18):2992–2998. doi:10.1200/JCO.2007.15.9947
139. Zhu AX, Holalkere NS, Muzikansky A, Horgan K, Sahani DV. Early antiangiogenic activity of bevacizumab evaluated by computed tomography perfusion scan in patients with advanced hepatocellular carcinoma. *Oncologist*. 2008;13(2):120–125. doi:10.1634/theoncologist.2007-0174
140. Hayano K, Lee SH, Yoshida H, Zhu AX, Sahani DV. Fractal analysis of CT perfusion images for evaluation of antiangiogenic treatment and survival in hepatocellular carcinoma. *Acad Radiol*. 2014;21(5):654–660. doi:10.1016/j.acra.2014.01.020
141. Lassau N, Koscielny S, Chami L, et al. Advanced hepatocellular carcinoma: early evaluation of response to bevacizumab therapy at dynamic contrast-enhanced US with quantification--preliminary results. *Radiology*. 2011;258(1):291–300. doi:10.1148/radiol.10091870
142. Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2006;24(12):1898–1903. doi:10.1200/JCO.2005.04.9130
143. Hsu CH, Kang YK, Yang TS, et al. Bevacizumab with erlotinib as first-line therapy in Asian patients with advanced hepatocellular carcinoma: a multicenter phase II study. *Oncology*. 2013;85(1):44–52. doi:10.1159/000350841
144. Hsu CH, Yang TS, Hsu C, et al. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. *Br J Cancer*. 2010;102(6):981–986. doi:10.1038/sj.bjc.6605580
145. Choi Y, Jung K. Normalization of the tumor microenvironment by harnessing vascular and immune modulation to achieve enhanced cancer therapy. *Experiment Mol Med*. 2023;55(11):2308–2319. doi:10.1038/s12276-023-01114-w
146. Ouyang X, Yao L, Liu G, Liu S, Gong L, Xiao Y. Loss of androgen receptor promotes HCC invasion and metastasis via activating circ-LNPEP/miR-532-3p/RAB9A signal under hypoxia. *Biochem Biophys Res Commun*. 2021;557:26–32. doi:10.1016/j.bbrc.2021.02.120
147. Husain A, Chiu YT, Sze KM, et al. Ephrin-A3/EphA2 axis regulates cellular metabolic plasticity to enhance cancer stemness in hypoxic hepatocellular carcinoma. *J Hepatol*. 2022;77(2):383–396. doi:10.1016/j.jhep.2022.02.018
148. Fan L, Tian C, Yang W, et al. HKDC1 promotes liver cancer stemness under hypoxia via stabilizing beta-catenin. *Hepatology*. 2024;81(6):1685–1699. doi:10.1097/HEP.0000000000001085
149. Shan Q, Yin L, Zhan Q, et al. The p-MYH9/USP22/HIF-1alpha axis promotes lenvatinib resistance and cancer stemness in hepatocellular carcinoma. *Sig Transduct Targeted Ther*. 2024;9(1):249. doi:10.1038/s41392-024-01963-5
150. Loong JH, Wong TL, Tong M, et al. Glucose deprivation-induced aberrant FUT1-mediated fucosylation drives cancer stemness in hepatocellular carcinoma. *J Clin Invest*. 2021;131(11). doi:10.1172/JCI143377
151. Zhang G, Zhang K, Zhao Y, Yang Q, Lv X. A novel stemness-hypoxia-related signature for prognostic stratification and immunotherapy response in hepatocellular carcinoma. *BMC Cancer*. 2022;22(1):1103. doi:10.1186/s12885-022-10195-1
152. Viallard C, Larrivee B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis*. 2017;20(4):409–426. doi:10.1007/s10456-017-9562-9
153. Wang W, Li T, Cheng Y, et al. Identification of hypoxic macrophages in glioblastoma with therapeutic potential for vasculature normalization. *Cancer Cell*. 2024;42(5):815–832e812. doi:10.1016/j.ccell.2024.03.013
154. Yang J, Guo Z, Song M, et al. Lenvatinib improves anti-PD-1 therapeutic efficacy by promoting vascular normalization via the NRP-1-PDGFRbeta complex in hepatocellular carcinoma. *Front Immunol*. 2023;14:1212577. doi:10.3389/fimmu.2023.1212577
155. Li B, Xu D, Zhou J, et al. Monitoring bevacizumab-induced tumor vascular normalization by intravoxel incoherent motion diffusion-weighted MRI. *J Magn Reson Imaging*. 2022;56(2):427–439. doi:10.1002/jmri.28012
156. Gerstner ER, Zhang Z, Fink JR, et al. ACRIN 6684: assessment of tumor hypoxia in newly diagnosed glioblastoma using 18F-FMISO PET and MRI. *Clin Cancer Res*. 2016;22(20):5079–5086. doi:10.1158/1078-0432.CCR-15-2529
157. Bekaert L, Valable S, Lechapt-Zalcman E, et al. 18F]-FMISO PET study of hypoxia in gliomas before surgery: correlation with molecular markers of hypoxia and angiogenesis. *Eur J Nucl Med Mol Imaging*. 2017;44(8):1383–1392. doi:10.1007/s00259-017-3677-5
158. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502. doi:10.1016/S0140-6736(17)31046-2

159. Bang YJ, Golan T, Dahan L, et al. Ramucirumab and durvalumab for previously treated, advanced non-small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: an open-label, phase Ia/b study (JVDJ). *Eur J Cancer*. 2020;137:272–284. doi:10.1016/j.ejca.2020.06.007
160. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the checkmate 040 randomized clinical trial. *JAMA oncol*. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
161. Melero I, Yau T, Kang YK, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040. *Ann Oncol*. 2024;35(6):537–548. doi:10.1016/j.annonc.2024.03.005
162. Sangro B, Galle PR, Kelley RK, et al. Patient-reported outcomes from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *J Clin Oncol*. 2024;42(23):2790–2799. doi:10.1200/JCO.23.01462
163. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
164. Salem R, Li D, Sommer N, et al. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: results from the IMbrave150 trial. *Cancer Med*. 2021;10(16):5437–5447. doi:10.1002/cam4.4090
165. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862–873. doi:10.1016/j.jhep.2021.11.030
166. Xia Y, Tang W, Qian X, et al. Efficacy and safety of camrelizumab plus apatinib during the perioperative period in resectable hepatocellular carcinoma: a single-arm, open label, phase II clinical trial. *J Immunother Cancer*. 2022;10(4):e004656. doi:10.1136/jitc-2022-004656
167. Zhang W, Tong S, Hu B, et al. Lenvatinib plus anti-PD-1 antibodies as conversion therapy for patients with unresectable intermediate-advanced hepatocellular carcinoma: a single-arm, phase II trial. *J Immunother Cancer*. 2023;11(9):e007366. doi:10.1136/jitc-2023-007366
168. Hsu C, Chang YF, Yen CJ, Xu YW, Dong M, Tong YZ. Combination of GT90001 and nivolumab in patients with advanced hepatocellular carcinoma: a multicenter, single-arm, phase 1b/2 study. *BMC Medicine*. 2023;21(1):395. doi:10.1186/s12916-023-03098-w
169. Li J, Bai Y, Chen Z, et al. SAFFRON-104: a phase Ib/II study of sitravatinib alone or with tislelizumab in advanced hepatocellular carcinoma and gastric cancer/gastroesophageal junction cancer. *Cancer Immunol Immunother*. 2024;73(11):219. doi:10.1007/s00262-024-03806-2
170. Ning T, Li D, Deng T, et al. Anti-PD-L1 antibody TQB2450 combined with tyrosine kinase receptor inhibitor AL2846 for immunotherapy-refractory advanced hepatocellular carcinoma and esophageal squamous cell carcinoma: a prospective phase 1b cohort study. *Cancer*. 2024;130(18):3137–3146. doi:10.1002/cncr.35377
171. Huynh JC, Cho M, Monjazeb A, et al. Phase I/II trial of BMS-986,205 and nivolumab as first line therapy in hepatocellular carcinoma. *Invest New Drugs*. 2024;42(1):35–43. doi:10.1007/s10637-023-01416-w
172. Wang K, Xiang YJ, Yu HM, et al. Adjuvant sintilimab in resected high-risk hepatocellular carcinoma: a randomized, controlled, Phase 2 trial. *Nat Med*. 2024;30(3):708–715. doi:10.1038/s41591-023-02786-7