Bridging Immune Evasion and Vascular Dynamics for Novel Therapeutic Frontiers in Hepatocellular Carcinoma

Sulin Wu [ID], Namrata Anand [ID], Zhoubo Guo, Mingyang Li, Marcos Santiago Figueroa [ID], Lauren Jung, Sarah Kelly and Joseph W. Franses *

Section of Hematology and Oncology, Department of Internal Medicine, University of Chicago, 900 E. 57th St., KCBD 7114, Chicago, IL 60637, USA; sulin.wu@uchicagomedicine.org (S.W.); namrata.anand@bsd.uchicago.edu (N.A.); zhoubo.guo@bsd.uchicago.edu (Z.G.); milingrid@bsd.uchicago.edu (M.L.); marcos.santiagofigueroa@bsd.uchicago.edu (M.S.F.); lauren.jung@bsd.uchicago.edu (L.J.); skkelly@uchicago.edu (S.K.)
* Correspondence: joseph.franses@bsd.uchicago.edu; Tel.: +1-773-834-5662

Simple Summary: Hepatocellular carcinoma (HCC) arises within a complex milieu of interacting cells and signaling elements. Modern medical therapies for HCC target the dysfunctional immune cells and vascular endothelial cells. This review summarizes mechanistic studies and enabling technologies of the HCC tumor microenvironment that can inform subsequent biomarker and therapeutic development.

Abstract: Hepatocellular carcinoma (HCC) remains one of the most lethal cancers globally, driven by chronic liver disease and a complex tumor microenvironment (TME). Recent advances in spatial omics, single-cell analyses, and AI-driven digital pathology have shed light on the intricate heterogeneity of HCC, highlighting key roles for immune suppression, angiogenesis, and fibrosis in tumor progression. This review synthesizes current epidemiological trends, noting a shift from viral hepatitis to metabolic syndrome as a primary etiology in Western populations, and elucidates how TME components—such as tumor-associated macrophages, cancer-associated fibroblasts, vascular endothelial cells, and immunosuppressive cytokines—contribute to resistance against conventional therapies. We detail the evolution of immunotherapeutic strategies from monotherapy to combination regimens, including dual immune checkpoint blockade and the integration of antiangiogenic agents. Emerging circulating and tissue-based biomarkers offer promise for enhanced patient stratification and real-time monitoring of treatment responses. Collectively, these innovations herald a paradigm shift toward TME-directed precision oncology in HCC, emphasizing the need for multi-targeted approaches to synergistically modulate interacting cellular constituents and ultimately improve clinical outcomes.

Keywords: hepatocellular carcinoma; tumor microenvironment; immune tolerance; angiogenesis; translational therapeutics

1. Introduction

Hepatocellular carcinoma (HCC) stands as one of the most lethal cancers worldwide, largely due to its intricate tumor biology and the profound influence of its unique tumor microenvironment (TME) [1]. Such TME changes share diverse origins in distinct chronic liver diseases—such as viral hepatitis, alcohol-related liver injury, and the increasingly prevalent metabolic-associated steatohepatitis (MASH)—leading to shared terminal carcinogenesis

pathways [2]. Therefore, HCC is recognized not only for its diverse etiologies but also for the complex interplay of cellular and molecular processes that govern its progression.

Recent advances in high-resolution profiling technologies have considerably refined our understanding of HCC. Spatial omics techniques, single-cell analyses, and artificial intelligence (AI)-driven platforms are unveiling the multifaceted nature of the TME, where interactions among cancer cells, immune infiltrates, stromal components, and extracellular matrix elements orchestrate tumor growth, angiogenesis, and resistance to immune attack. These insights, along with evolving liquid biopsy strategies and multi-omics biomarker panels, are steering the field toward non-genomic precision oncology approaches.

This review summarizes the global epidemiological trends, the cellular and molecular landscape of the HCC TME, and the latest clinical advances in immunotherapy and combination treatments. We explore key aspects of HCC, from the shifting etiological factors and regional disparities in incidence and survival to the specialized roles of various cell types in the TME. Furthermore, we delve into the emerging paradigm of spatially resolved, AI-enhanced analyses that have begun to unravel the complexities of tumor heterogeneity and resistance mechanisms, setting the stage for the development of next-generation therapies. In highlighting major clinical trials, we emphasize how novel strategies, such as dual immune checkpoint inhibition and immune checkpoint inhibition combined with antiangiogenic agents, are beginning to overcome the entrenched resistance within the TME. Looking forward, we discuss the challenges and future directions in HCC treatment, focusing on innovative therapeutic targets, cutting-edge preclinical models, and the potential of integrating spatial multi-omics with digital analytics to help achieve durable responses.

Through this overview, we aim to provide a cohesive narrative that connects epidemiological shifts, mechanistic insights, and clinical breakthroughs, ultimately charting a path toward transforming HCC from a historically intractable malignancy into a disease with more manageable outcomes.

2. Global Epidemiological Landscape

Regions with endemic hepatitis B and C virus (HBV and HCV, respectively) infections continue to bear the highest burden of HCC [3]. However, the epidemiological profile is shifting in Western countries (Table 1). In the United States, for instance, metabolic syndrome and its associated metabolic-associated fatty liver disease (MAFLD), metabolic-associated steatohepatitis (MASH), and alcohol-related liver disease have overtaken viral etiologies. Recent improved outcomes in the U.S., with a 5-year survival rate of 21.3%-reflect advances in surveillance, early detection, and multi-disciplinary treatment strategies [4,5].

This epidemiological shift underscores a broader global trend, where rising rates of obesity and type 2 diabetes have propelled metabolic dysfunction to the forefront of HCC etiology, both in the West and in the rest of the world. Recent data indicate that up to 40% of HCC cases in the United States and the European Union are linked to metabolic dysfunction, and importantly, many of these cases emerge in patients without significant cirrhosis [6]. Although hepatitis B still dominates as the leading cause of HCC in most Asian countries, the increasing prevalence of metabolic syndrome—exceeding 30% in some regions such as Japan and South Korea—has begun to shift the disease landscape toward MAFLD-related HCC [7,8]. In the Middle East and North Africa, high diabetes prevalence, reaching around 18% in certain countries, has further fueled the rise of MAFLD-driven HCC [9].

Notably, the occurrence of up to half of MAFLD-related HCC cases in non-cirrhotic livers can often lead to delay of diagnosis until advanced stages, when curative-intent treatments are no longer available. By 2030, MAFLD/MASH is projected to become the leading cause of HCC in the United States and Europe [10,11]. Consequently, there is

a growing consensus on the need for enhanced surveillance and earlier intervention in patients at risk. Further, public health strategies targeting obesity, diabetes, and excessive alcohol consumption are critical to improve early detection and intervention.

In summary, while viral hepatitis remains a primary cause of HCC in low- and middle-income countries, where antiviral treatments and vaccination programs have begun to reduce the incidence, MAFLD/MASH has emerged as the second most common and fastest-growing etiology worldwide. These epidemiological shifts underscore the urgent need for tailored public health strategies and clinical interventions to address the evolving landscape of HCC [12].

Table 1. Epidemiology of Hepatocellular Carcinoma (HCC) in the United States vs. Global Data [1,5,13–16].

Parameter	United States (US)	Global (WHO Data)
Incidence Rate	Approximately 6–8 cases per 100,000 people annually	Approximately 110–20 cases per 100,000 people globally (varies widely by region)
Annual New Cases	≈12.5 per 100,000 population new cases (projected for 2024)	≈11.2 per 100,000 population new cases globally
Leading Risk Factors	Hepatitis C infection, alcohol-related liver disease, metabolic-associated fatty liver disease (MAFLD)/MASH	Hepatitis B and C infections, aflatoxin exposure, metabolic-associated liver disease, MAFLD
Most Affected Age Group	50–70 years	Varies by region; generally, affects individuals aged 40–70 years
Gender Distribution	Male—Female ≈ 2–3:1	Male—Female ≈ 2–4:1 (higher male predominance in HBV-endemic regions)
Five-Year Survival Rate	~20% for localized HCC, ~11% overall	~18% globally (varies widely by region and stage at diagnosis); <10% in high-burden regions (due to late diagnosis, limited treatment access)
Primary Etiological Agents	Hepatitis C (historically the most common), but MAFLD and metabolic syndrome-related HCC rates are rising	Hepatitis B is the leading cause globally, especially in Asia and Africa; rising cases from MAFLD in Western countries
Mortality Rate	≈9.3 per 100,000 population deaths annually	≈10.2 per 100,000 population deaths globally annually
Regional Hotspots	Highest incidence rates in Southern and Southwestern states	High-incidence regions include East Asia (China), Southeast Asia, sub-Saharan Africa, and parts of the Middle East
Trends	Increasing due to MAFLD and obesity, especially in younger populations, historically driven by hepatitis C	Rising in Western countries due to MAFLD; stabilized or decreasing in regions with effective hepatitis B vaccination
Screening and Early Detection	Routine screening for high-risk individuals (e.g., those with cirrhosis and hepatitis B/C) is increasing	Varies by region; established in some high-risk areas (e.g., Asia); less common in low-resource settings

3. Tumor Microenvironment Landscape in HCC

Hepatocellular carcinoma (HCC) arises within the unique immunological context of the liver, an organ naturally inclined to maintain a delicate equilibrium between immune surveillance and tolerance. While this tolerogenic state is essential for limiting inflammation in response to dietary and microbial antigens, it can become a liability when exploited by malignant cells to evade immune destruction.

HCC typically develops through a stepwise progression initiated by chronic liver injury and sustained inflammation, leading to fibrosis and malignant transformation [17]. Persistent activation of hepatic stellate cells (HSCs) promotes excessive extracellular matrix (ECM) deposition and fibrotic remodeling. This fibrogenic response, combined with cytokine signaling and immune cell infiltration, fosters a pro-tumorigenic microenvironment that supports HCC progression (Figure 1) [18–20].
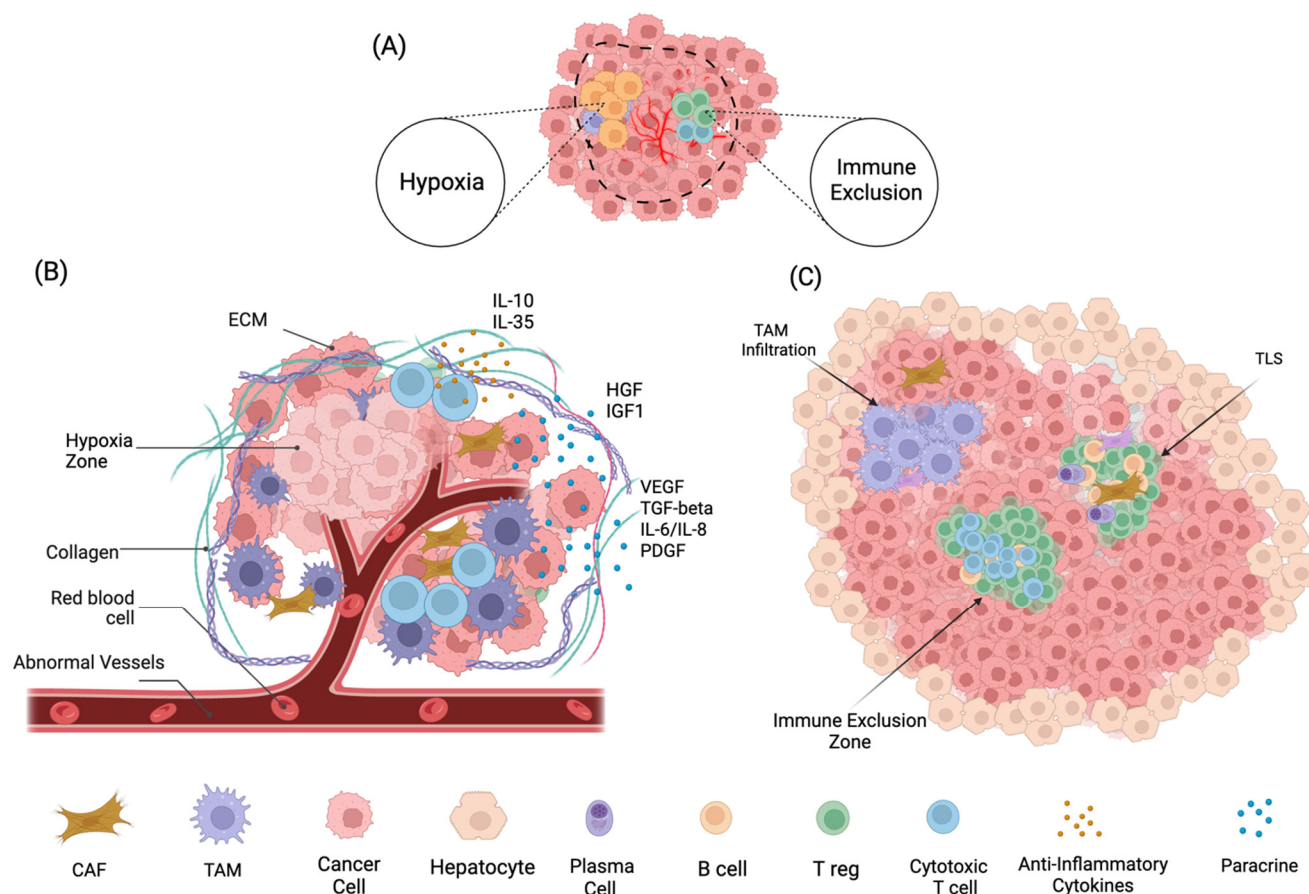

Figure 1. Spatial and Cellular Heterogeneity of the Tumor Microenvironment in Hepatocellular Carcinoma. This illustration highlights key structural and cellular components of the hepatocellular carcinoma (HCC) tumor microenvironment (TME) across different spatial contexts. (A) Schematic overview of the tumor ecosystem depicting disorganized vasculature, abundant stromal fibroblasts, and diverse immune cell infiltration. This cross-sectional illustration of an HCC tumor highlights the complex interactions among tumor cells, immune populations, fibroblasts, abnormal blood vessels, and the extracellular matrix (ECM), which collectively shape the immune microenvironment, drive tumor progression and present opportunities for therapeutic targeting. (B) Abnormal and leaky vasculature contributes to hypoperfusion and hypoxia, impairing immune cell function and promoting extracellular matrix (ECM) remodeling. The perivascular niche is defined by disorganized vessels, collagen deposition, and infiltration of immune cells—including lymphocytes and myeloid-derived suppressor cells—embedded within the ECM. Additional components such as red blood cells (RBCs), stromal fibroblasts, and tertiary lymphoid structures (TLSs) shape the immunomodulatory landscape and influence tumor progression. (C) TLSs are organized aggregates of immune cells resembling lymph nodes, typically forming at tumor margins. Immune exclusion refers to the restricted infiltration of cytotoxic T-cells and other effector immune cells into the tumor core, often due to fibrotic stroma, abnormal vasculature, or immunosuppressive cells. Within the tumor mass, dense clusters of tumor cells are surrounded by exclusion zones and focal TLSs. These barriers may limit immune cell access and reduce the efficacy of immunotherapies.

The liver's specialized sinusoidal architecture, featuring fenestrated endothelial cells and minimal basement membrane, facilitates continuous interaction between hepatocytes, endothelial cells, immune cells, and gut-derived antigens. In chronic liver disease, this homeostatic balance is disrupted. Hallmarks such as hypoxia and fibrosis drive stabilization of HIF-1α, which induces proangiogenic signaling and the formation of disorganized, leaky vasculature. These vascular abnormalities impair immune cell infiltration and reinforce immunosuppressive signaling [21,22]. Simultaneously, stromal activation contributes to matrix remodeling, immune exclusion, and therapeutic resistance through dense ECM deposition and paracrine signaling [23,24].

The tumor microenvironment (TME) in HCC is thus shaped by a complex interplay of immune, stromal, and vascular components that collectively drive tumor progression and limit therapeutic efficacy. Among these, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), regulatory T-cells (Tregs), and tertiary lymphoid structures (TLS) represent key cellular populations that orchestrate immune suppression, matrix dynamics, and spatial immune patterning (Table 2). The following sections explore the distinct yet interconnected functions of these cells and their roles in shaping the immuno-suppressive, fibrotic, and angiogenic landscape of liver cancer.

Table 2. Key Cell Types in the Tumor Microenvironment (TME) of HCC Compared to Other Solid Tumors.

Cell Type	HCC TME Role	Key Differences in Other Tumors
Cancer-Associated Fibroblasts (CAFs)	Drive fibrosis, immunosuppression, and angiogenesis via TGF-β and HGF; contribute to a dense, fibrotic microenvironment.	Fibrosis is less extensive; CAFs less central in shaping TME.
Tumor-Associated Macrophages (TAMs)	Predominantly M2-polarized; secrete IL-10, VEGF, and TGF-β; promotes immune evasion and angiogenesis.	TAMs are less M2-polarized and not as strongly shaped by liver-induced immune suppression.
Endothelial Cells	Form abnormal, leaky vasculature due to VEGF and hypoxia; enhance hypoxia and limit immune infiltration.	Vascular remodeling is less hypoxia-driven and more structured angiogenesis.
Regulatory T-cells (Tregs)	Abundant due to liver's immune tolerance; suppress CD8+ T cells and promote immune evasion.	Lower baseline Treg levels and less impact on TME.
CD8+ T Cells	Exhausted or dysfunctional; impaired cytotoxicity due to inflammation and high PD-1 expression.	More functional CD8+ T cells; less exhaustion.
Natural Killer (NK) Cells	Reduced activity due to tolerogenic liver environment and hypoxia limits cytotoxic potential.	NK cells are more active; less suppression by hypoxia or TGF-β.
Myeloid-Derived Suppressor Cells (MDSCs)	Abundant due to inflammation; suppress T-cell activity and enhance immune suppression.	Lower frequency and suppressive capacity of MDSCs.
Extracellular Matrix (ECM)	Densely fibrotic due to liver disease, it forms a physical barrier to immune cells and promotes tumor spread.	ECM remodeling is driven by tumor cells, not pre-existing fibrosis.

In HCC tumors, tumor-associated macrophages (TAMs) predominantly exhibit an M2-like phenotype, secreting vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and interleukin-10 (IL-10) to suppress cytotoxic T-cell activity and to facilitate pathologic angiogenesis. Several linked mechanisms reinforce these tumor-promoting behaviors. First, the cleavage of FNDC5 into irisin activates peroxisome proliferator-activated receptor gamma (PPARγ) in TAMs, helping maintain their M2-like state [25]. Second, tumor-derived CCL16 recruits CCR1/CCR5+ monocytes, which differentiate into immunosuppressive TAMs [26]. Finally, the upregulation of matrix metalloproteinase 21 (MMP21) in HCC cells triggers the production of colony-stimulating factor 1 (CSF-1) and fibroblast growth factor 1 (FGF-1), creating a chemotactic gradient for TAM infiltration [27]. Together, these pathways form a self-reinforcing loop that protects tumors from immune surveillance while driving metastatic spread. Beyond their immunosuppressive role, TAMs contribute to ECM remodeling and fibrosis through the secretion of TGF-β and matrix metalloproteinases, linking immune evasion to physical barriers that hinder T-cell infiltration, as noted in various cancers [28,29].

Cancer-associated fibroblasts (CAFs) play a pivotal role in remodeling HCC's fibrotic tumor microenvironment (TME), both physically and biochemically impeding immune cell infiltration. Activated by TGF-β and PDGF, CAFs secrete dense extracellular matrix (ECM) components such as collagen and periostin (POSTN), effectively blocking cytotoxic T-cells [24]. They also promote therapeutic resistance via paracrine signaling. For instance, CAF-derived exosomes carry oncogenic microRNAs (e.g., miR-1228-3p, miR-20a-5p) that activate the PI3K/AKT and Wnt/β-catenin pathways in HCC cells, reducing sorafenib sensitivity [30,31]. Similarly, secreted phosphoprotein 1 (SPP1) from CAFs diminishes the effectiveness of tyrosine kinase inhibitors (TKIs) by upregulating folate receptor alpha (FOLR1) in tumor cells [32,33]. Furthermore, emerging spatial metabolomics research has identified specialized ECM metabolic niches that actively drive tumor progression and shape therapy response [34–39]. CAFs also amplify proangiogenic signaling in response to hypoxia, creating a fibrotic niche that enhances resistance to therapy and supports tumor expansion [23,40].

Regulatory T-cells (Tregs) are key mediators of the immunosuppressive microenvironment in HCC. Enriched particularly in HBV-associated cases, Tregs contribute to immune evasion and tumor progression [41]. They are defined by CD4, CD25, and Foxp3 expression and exert suppressive effects through multiple mechanisms. Tregs inhibit cytotoxic T-cells via inhibitory cytokines (IL-10, IL-35), contact-dependent suppression (CTLA-4, PD-1), and metabolic disruption, such as IL-2 consumption and adenosine production [42]. They are recruited to the tumor through CCR4/CCR6-mediated chemotaxis in response to CCL22 and CCL20, with transcription factors like GATA4 and SOX12 upregulating these ligands [43,44]. In HBV-related HCC, Tregs often display a tissue-resident phenotype and induce apoptosis in effector T-cells via FASLG–FAS interactions [42,45,46].

Tumor-infiltrating Tregs also exhibit enhanced survival and suppressive activity due to epigenetic remodeling [42,45,47]. Clinically, high Treg density correlates with poor prognosis and resistance to therapies, including immune checkpoint inhibitors and sorafenib [41,46,48,49]. Targeting Treg pathways, including CCR4 or CD177, represents a promising strategy to enhance antitumor immunity [44,50–52].

While Tregs exemplify cellular mechanisms of immune suppression, the structural organization of immune cells within the tumor microenvironment, such as the formation of tertiary lymphoid structures (TLS), adds another layer of complexity in shaping immune responses and prognosis in HCC [53–55]. TLS are ectopic lymphoid aggregates found in some HCCs containing CD8+ T cells, B cells, and LAMP3+ dendritic cells. However, the presence of TLS alone does not consistently predict therapeutic response. Spatial

transcriptomic studies reveal that TLS function is contingent on stromal cues. For example, CCL10+ fibroblasts may collaborate with plasma cells (IGHG1+) to recruit T cells, creating immune-active niches, whereas DKK1+ tumor cells can inhibit CCL19+ lymphoid cell infiltration [56,57]. Thus, TLS in HCC correlates with immune therapy responses, but such responses are still dependent on the broader TME context. As the tumor expands, increased metabolic demands and disorganized vasculature lead to localized hypoxia. Hypoxia stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), which upregulates VEGF and other angiogenic factors to promote abnormal vessel formation. These malformed vessels limit immune cell access while further enhancing hypoxia, creating a self-sustaining cycle of immunosuppression and resistance [58–61].

Emerging Therapeutic Implications in Remodeling HCC TME

The therapeutic landscape for HCC is rapidly evolving to address the multifaceted challenges posed by its microenvironment. One promising avenue lies in targeting cancer-associated fibroblasts (CAFs). By inhibiting key signaling molecules such as SPP1 and CXCL12 or even by interfering with exosome release, researchers hope to disrupt the paracrine communication that fosters antiangiogenic TKI resistance and promotes tumor survival [32,62–65]. The reprogramming of tumor-associated macrophages (TAMs) to a more M1-like state is another compelling area of research. Recent studies suggest that modulating pathways like FNDC5/irisin or chemokine receptors such as CCR1/CCR5 could shift TAMs away from their pro-tumorigenic M2-like state toward a phenotype more conducive to antitumor immunity [25,66,67].

Another critical frontier involves the selective depletion or functional modulation of Tregs, particularly by targeting the CCL22-CCR4 or FASLG-FAS signaling axes [44,50,68,69]. These approaches aim to rejuvenate CD8+ T cell responses, which are often exhausted by multiple factors in the HCC TME. Recognizing the unique immunological niche of the liver, researchers are increasingly integrating spatial omics and patient-derived models to decipher context-specific interactions within the TME. This comprehensive strategy not only underscores the need for multi-targeted interventions but also offers a roadmap for exploiting the liver's dual capacity for immune tolerance and surveillance to ultimately enhance therapeutic efficacy in HCC.

4. Angiogenesis Signaling in HCC

Angiogenesis in HCC is driven by a complex interplay of cytokines, growth factors, and hypoxia-induced signaling that promotes abnormal vascularization and immune evasion [70]. A hallmark of the HCC TME is hypoxia, which stabilizes HIFs, particularly HIF-1α—a master transcription factor that upregulates key proangiogenic mediators such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [61,71–76]. Overexpression of these molecules drives endothelial proliferation and disorganized, leaky blood vessel formation, creating nutrient-rich but immunosuppressive niches (Figure 2) [21,73,75,76]. These malformed vessels exacerbate hypoxia and contribute to a self-perpetuating cycle of tumor progression. Excess VEGF, for example, inhibits dendritic cell maturation and recruits myeloid-derived suppressor cells (MDSCs), enhancing immune evasion [77–79].
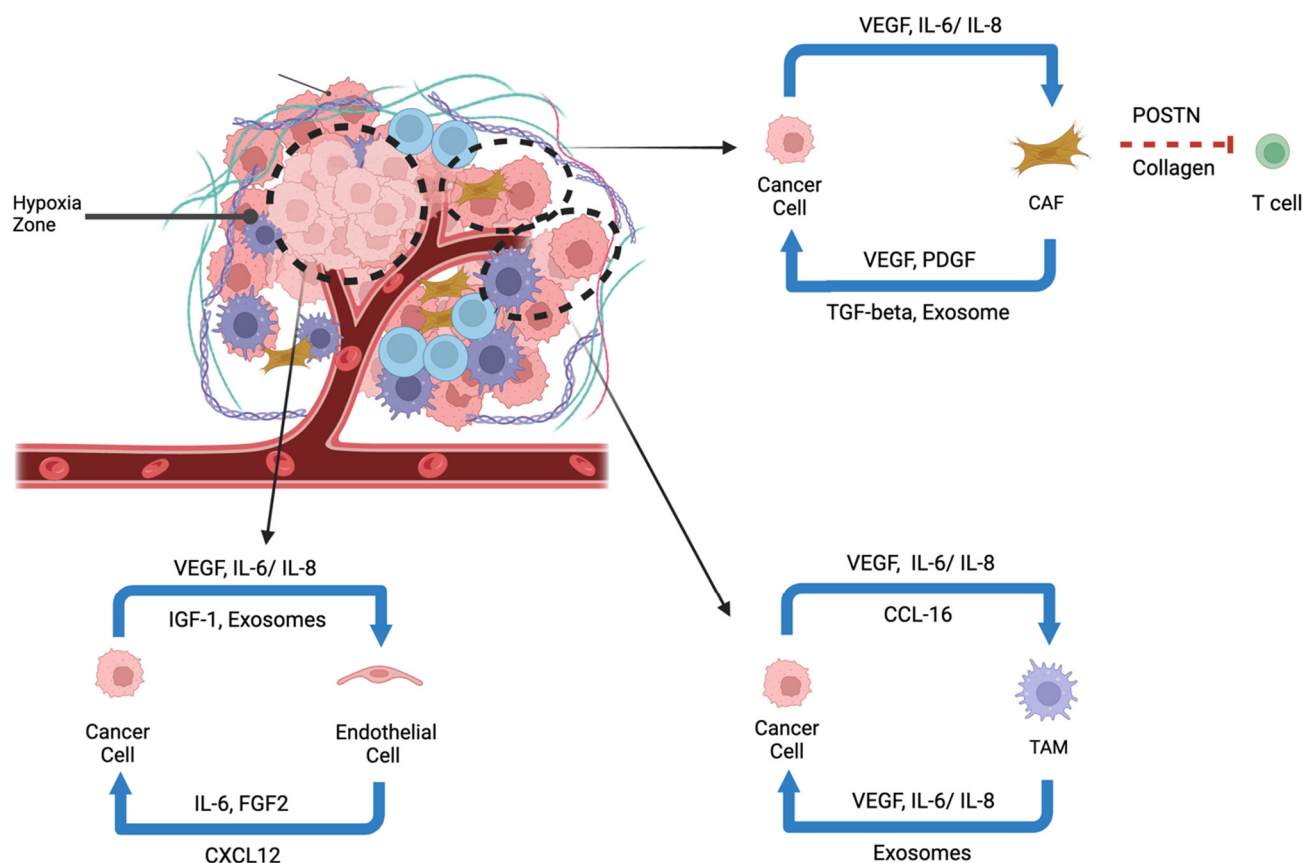
Figure 2. Cytokine and Growth Factor-Mediated Cellular Crosstalk in the Hypoxic Tumor Microenvironment of Hepatocellular Carcinoma. The schematic illustrates cytokine-mediated interactions among cancer cells, endothelial cells, cancer-associated fibroblasts (CAFs), and tumor-associated macrophages (TAMs) in the hypoxic tumor microenvironment of hepatocellular carcinoma (HCC). Cancer cells secrete VEGF, IL-6, and IL-8 to activate endothelial cells (via IGF-1, exosomes) and CAFs (via VEGF, PDGF, TGF-β, exosomes). CAFs contribute to extracellular matrix remodeling through POSTN and collagen, impeding T-cell infiltration. TAMs are recruited via CCL-16 and maintain tumor-promoting loops through VEGF, IL-6, IL-8, and exosomes. These reciprocal interactions support angiogenesis, immune evasion, and tumor progression.

While HIF-1α is the most extensively studied isoform, growing evidence highlights the role of HIF-2α in regulating angiogenesis and tumor progression in specific HCC subtypes [80–83]. Preclinical studies have demonstrated that HIF-2α inhibitors, such as PT2385, effectively suppress angiogenic pathways and inhibit tumor progression in HCC models [84,85]. Building upon these findings, clinical investigations are underway to evaluate the efficacy of HIF-2α inhibitors in HCC treatment. Additionally, isoform-specific HIF-2α antisense oligonucleotides (ASOs) have been investigated experimentally in HCC mouse models. These ASOs effectively downregulated HIF-2α expression; however, they did not significantly impact tumor numbers and, in some cases, even aggravated liver fibrosis, highlighting the complexity of therapeutically targeting HIF-2α in HCC [86]. Notably, a Phase I/II clinical trial (NCT04976634) is assessing the safety and efficacy of Belzutifan (MK-6482), a selective HIF-2α inhibitor [46], in combination with Lenvatinib, a tyrosine kinase inhibitor, for patients with advanced HCC. This study aims to clarify the potential benefits and limitations of HIF-2α inhibitors as adjunct therapies, particularly in HCC subtypes characterized by elevated HIF-2α expression. These clinical efforts reflect a growing interest in targeting HIF-2α as a therapeutic strategy to improve outcomes for patients with advanced HCC.

Angiogenic signaling in HCC arises from both local (paracrine) and systemic (endocrine) sources [75,87]. Within the TME, tumor cells and stromal components, including CAFs and TAMs, secret VEGF, IL-6, IL-8, and matrix metalloproteinases promote vessel formation and remodeling [88–93]. CAF-derived PDGF recruits pericytes to stabilize nascent vessels; however, this often results in increased vascular permeability and metastatic potential [88,90,91,94]. Importantly, endothelial cells can also emit "angiocrine" regulatory signals to other stromal or even cancer cells in the TME [95]. Deeper insights into this additional layer of function are relatively underexplored but may lead to additional functional vascular targets in the HCC TME.

Systemically, endocrine factors also sustain angiogenesis. Transforming growth factor-beta (TGF-β) induces endothelial-to-mesenchymal transition (EMT), generating hybrid endothelial cells that facilitate vessel co-option [96–99]. Additionally, insulin-like growth factor-1 (IGF-1) promotes endothelial proliferation through PI3K/AKT signaling while downregulating thrombospondin-1 (TSP-1), an antiangiogenic molecule [100–102]. Together, these localized and systemic cues create a proangiogenic environment that supports tumor growth, metastasis, and therapy resistance (Figure 1).

Beyond soluble cytokines and growth factors, recent studies have identified extracellular vesicles, particularly exosomes, as critical mediators that integrate angiogenic and immunosuppressive signals within the HCC microenvironment [103–106]. These vesicles offer a distinct mechanism of intercellular communication, complementing classical paracrine and endocrine pathways. These nano-sized vesicles, secreted by both tumor and stromal cells, contain diverse molecular cargo such as cytokines, microRNAs, and proteins, representing a distinct mechanism of intercellular communication that complements soluble factor signaling (Table 3).

Table 3. Key Paracrine and Exosomal Mediators in HCC.

	Factor	Source	Mechanism
Paracrine	VEGF	Tumor cells, CAFs	Binds VEGFR2 to induce endothelial proliferation and vascular permeability.
	IL-6/IL-8	TAMs, HCC cells	Activates STAT3 in endothelial cells, enhancing survival and MMP expression.
	PDGF	CAFs	Recruits pericytes to stabilize nascent vessels, albeit abnormally, fostering leaky vasculature that facilitates metastasis.
	HGF	Stromal cells, plasma	Triggers c-MET signaling to promote vascular mimicry and metastasis.
	TGF-β	CAFs, Tregs	Induces EndMT, enabling vessel co-option and immune evasion.
	IGF-1	Tumor cells	promotes endothelial proliferation via PI3K/AKT signaling, while suppressing antiangiogenic thrombospondin-1 (TSP-1).
Exosomal Cargo	PD-L1	Tumor cells	Suppresses T-cell activation to promote immune evasion. Potential biomarker for immunosuppression.
	miR-210	Tumor cells	Suppresses Ephrin-A3, destabilizing endothelial junctions to aid intravasation. Associated with increased vascularization.
	miR-122	Tumor cells	Regulates cell proliferation and modulates drug sensitivity. Investigated as a diagnostic/therapeutic response marker.
	miR-21	Tumor cells, TAMs	Enhances cell proliferation and invasion. Considered a prognostic marker for HCC progression.

Exosomes have emerged as key drivers of angiogenic reprogramming in HCC by facilitating crosstalk among tumor cells, stromal components, and pre-metastatic niches [107,108]. This contributes to the establishment of proangiogenic and immunosuppressive conditions that favor tumor progression. Notably, exosomal PD-L1 has been proposed as a potential diagnostic biomarker, reflecting the immunosuppressive dynamics of the HCC tumor [109–111]. In parallel, exosomal microRNAs have been implicated in forming proangiogenic niches that enhance neovascularization and metastatic potential [112–114]. By modulating both vascular and immune pathways, exosomes reinforce the complex interplay between angiogenesis and immune evasion in HCC, underscoring their relevance as both biomarkers and therapeutic targets.

5. Clinical Trials and Treatment Approaches Targeting TME and Angiogenesis

The evolution of HCC treatments over the past decade has not only redefined clinical strategies but also underscored the pivotal role of the tumor microenvironment (TME) in dictating therapeutic outcomes (Table 4). Initially, the introduction of sorafenib in 2007 marked a turning point. As a multikinase angiogenesis inhibitor targeting VEGFR, PDGFR, and RAF kinases, sorafenib demonstrated modest efficacy in the SHARP trial by extending overall survival from 7.9 (with placebo) to 10.7 months. However, its modest benefits and significant side effects demonstrated the need for more refined approaches. Subsequently, additional similar angiogenesis inhibition therapies were evaluated. Cabozantinib [115], regorafenib [116], and ramucirumab [117] offer some benefits after sorafenib treatment. Lenvatinib was found to be non-inferior but perhaps somewhat more easily tolerated than sorafenib [118]. These studies showed that the activity and durability of such monotherapies are often limited by the inability to counteract immune resistance mechanisms.

This recognition of the TME as a key modulator of treatment efficacy has led to the integration of immuno-oncology (IO) agents into therapeutic regimens. The pivotal IMbrave150 trial was the first phase 3 trial to demonstrate the potential synergy resulting from combined targeting of angiogenesis signaling and immune checkpoints [119]. The combination of atezolizumab, a PD-L1 inhibitor, with bevacizumab, an anti-VEGF antibody, showed significantly improved radiographic response rate, progression-free survival, and overall survival compared with sorafenib. Hence, normalizing the tumor vasculature can lead to reinvigorated T-cell function. Similarly, the APOLLO trial (presented in 2024 but not yet published) and CARES-310 trial [120] showed that the combination of antiangiogenic TKIs and PD-1 inhibitors can significantly outperform sorafenib, further reinforcing the value of combining IO with targeted therapies. However, other similar co-targeting strategies, including Lenvatinib plus pembrolizumab [121] or cabozantinib plus atezolizumab [122], did not exhibit similar synergy, pointing to the dynamic and nuanced nature of the HCC TME and the possibility of synergistic toxicity mitigating treatment benefits [123].

Simultaneous inhibition of two critical immune checkpoints—PD1/PD-L1 and the cytotoxic T-lymphocyte-associated protein 4 (CTLA4)/CD80-CD86—has also been explored. The HIMALAYA study [124] demonstrated a significant benefit of a single loading dose of tremelimumab combined with durvalumab, with a very durable benefit in a small but significant minority of treated patients [125]. Similarly, the CheckMate-9DW trial (presented in 2024, not yet published) has shown excellent survival benefits from the combination of ipilimumab (CTLA4 inhibitor) and nivolumab (PD-1 inhibitor)—compared with lenvatinib—despite concerns over a significant proportion of patients experiencing immune-related toxicities.

Table 4. Major Clinical Trials in Advanced HCC: Immunotherapy and Combination Approaches.

Category	Trial Name	Therapy Combination	Phase	PFS	OS	Key Findings
IO	CheckMate-040 [126]	Nivolumab (PD-1) + Ipilimumab (CTLA-4)	I/II	5.1 months vs. 4.3 months (nivolumab/ipilimumab plus cabozantinib)	20.2 months vs. 22.1 months for the triplet arm	Doublet demonstrates encouraging antitumor activity and consistent safety profiles for the combination therapies in patients with advanced HCC.
	KEYNOTE-224 [127–129]	Pembrolizumab (PD-1)	II	4 months (95% CI, 2–8)	13.9 months	Pembrolizumab monotherapy provides durable antitumor activity, promising overall survival, and has a manageable safety profile in patients with advanced HCC who have not received prior systemic therapy.
	KEYNOTE-240 [130–132]	Pembrolizumab (PD-1)	III	3.0 months vs. 2.8 months (placebo) HR 0.72	13.9 months vs. 10.6 months (placebo) HR of 0.78	Pembrolizumab provides clinical benefits in terms of antitumor activity and safety, supporting its use as a second-line therapy in advanced HCC despite not achieving statistical significance in primary endpoints.
Combination	KN046 [133]	KN046 (PD-L1/CTLA-4 bispecific antibody) monotherapy	II	11.0 months (95% CI, 8.2–15.2)	16.4 months (95% CI, 11.20-not estimable), 12-month OS rate of 60.0% (95% CI, 45.9–71.6)	KN046 combined with lenvatinib showed promising efficacy and a manageable safety profile in patients with advanced unresectable or metastatic HCC. The objective response rate (ORR) was 45.5% (95% CI, 31.97–59.45).
	INSPIRE [134]	Atezolizumab (anti-PD-L1) + Bevacizumab (anti-VEGF)	II	4.8 months	12.9 months	The study highlighted the potential of pembrolizumab as a therapeutic option for HCC, particularly in patients who have progressed on or are intolerant to sorafenib.
	HIMALAYA [135,136]	Durvalumab (PD-L1) + Tremelimumab (CTLA-4)	III	3.8 months (STRIDE) vs. 4.3 months (sorafenib)	16.4 months vs. 13.7 months (sorafenib)	These findings support the use of STRIDE as a novel first-line systemic therapy for unresectable HCC, demonstrating sustained long-term survival benefits and a favorable safety profile.
	IMbrave150 [119,137]	Atezolizumab (PD-L1) + Bevacizumab (VEGF)	III	6.8 months vs. 4.3 months (sorafenib) HR 0.59 (95% CI, 0.47 to 0.76)	19.2 months vs. 13.4 months (sorafenib) HR 0.66 (95% CI, 0.52 to 0.85)	Significant improvement in both PFS and OS, establishing a new first-line treatment standard in HCC. The combination therapy also delayed the deterioration of quality of life and functioning compared to sorafenib.

Table 4. *Cont.*

Category	Trial Name	Therapy Combination	Phase	PFS	OS	Key Findings
Combination	CARES-310 [120,138]	Camrelizumab (PD-1) + Rivoceranib (TKI)	III	5.6 months vs. 3.7 months (sorafenib) HR 0.52 (95% CI, 0.41–0.65; one-sided $p < 0.0001$)	22.1 months vs. 15.2 months (sorafenib) HR of 0.62 (95% CI, 0.49–0.80; one-sided $p < 0.0001$).	Demonstrated strong efficacy in PFS and OS, supporting IO-TKI combination as a new and effective first-line treatment option for unresectable HCC.
	CheckMate-9DW	Nivolumab (PD-1) + Cabozantinib (TKI)	III	Not Available	Not Available	Detailed results regarding these endpoints are not available in the current medical literature.
	LEAP-002 [121,135,139]	Pembrolizumab (PD-1) + Lenvatinib (TKI)	III	8.2 months vs. 8.0 months (lenvatinib plus placebo) HR 0.87 (95% CI, 0.73–1.02)	21.2 months vs. 19.0 months (lenvatinib plus placebo) HR 0.84 (95% CI, 0.71–1.00)	While the combination did not significantly improve survival outcomes, it highlighted the potential activity of lenvatinib plus pembrolizumab in advanced HCC with an objective response rate (ORR) of 26.3% for lenvatinib plus pembrolizumab versus 17.5% for lenvatinib plus placebo.

6. Spatial Omics and Biomarker Discovery for Precision Medicine in HCC

In addition to traditional approaches such as bulk RNA sequencing, single-cell RNA sequencing, and flow cytometry, emerging spatial profiling methods are emerging as powerful tools for understanding the TME [140]. Techniques spanning single-color immunohistochemistry (IHC), multiplex IHC (mIHC), imaging mass cytometry (IMC), CODEX, and spatial transcriptomics allow researchers to visualize the physical arrangement of interacting cellular subsets and their association with tumor progression, therapeutic resistance, and immune evasion [141]. These spatial insights have informed mechanistic studies and guided the discovery of patient-specific biomarkers.

Recent studies using spatial profiling have revealed substantial intratumoral heterogeneity (ITH) that impacts prognosis and treatment response [142]. Multi-regional sequencing shows that spatial distance correlates with transcriptomic diversity [143]. A composite ITH scoring system combining spatial and molecular data identified that low-ITH tumors express higher levels of CD40 and PD-L1 and are enriched in activated memory T-cells and natural killer (NK) cells, suggesting greater responsiveness to immune checkpoint blockade. In contrast, high-ITH tumors harbor more exhausted CD4^{+} and CD8^{+} T cells and correlate with worse clinical outcomes [144].

Spatial profiling has illuminated key interactions between tumor cells and stromal components that actively shape the immunosuppressive architecture of the HCC microenvironment. CAFs often co-localize with EpCAM[+] cancer stem cells (CSCs), promoting tumor cell stemness and aggressive phenotypes through direct contact and paracrine signaling [145]. Simultaneously, SPP1^{+} macrophages accumulate in hypoxic zones near CSC-rich regions, fostering a fibrotic, immunosuppressive environment that limits immune cell infiltration [146]. Together, SPP1^{+} macrophages and POSTN[+] CAFs form physical and biochemical tumor immune barriers (TIBs) that shield tumor cores from T-cell access and reduce the efficacy of immune checkpoint blockade (ICB) therapies [147]. Notably, the

blockade of SPP1 in preclinical models disrupts this barrier, restores immune infiltration, and improves ICB responsiveness [148,149].

Additional immunosuppressive structures involve specific macrophage and fibroblast populations that accumulate at tumor boundaries. FAP+ CAFs and DAB2+ TAMs co-localize at invasive margins in ICB non-responders, forming another type of stromal barrier that excludes cytotoxic lymphocytes [150]. TREM2+ macrophages, frequently located near exhausted CD8+ T cells, have been implicated in immune tolerance mechanisms and may serve as therapeutic targets. A combined anti-CSF1R and anti-PD1 blockade has shown synergistic antitumor effects in models with TREM2+ myeloid populations [151]. Moreover, spatial clustering of TAMs (TAM-high signatures, or TAMs-HS) around tumor nests correlates with poor T-cell infiltration and diminished responses to immunotherapy [152]. Vimentin-high macrophages, which frequently co-localize with Tregs and exhibit elevated inflammatory signaling, may further define an immunosuppressive macrophage subset with predictive value for ICB resistance [153].

The immune architecture of HCC also reflects developmental reprogramming, resembling the immunological state of the fetal liver. The "onco-fetal" phenotype, marked by POSTN+ CAFs, FOLR2+ TAMs, and PLVAP+ endothelial cells, promotes Treg recruitment and immunological tolerance via conserved embryonic signaling programs [154,155]. This developmental mimicry contributes to immune evasion and therapeutic resistance. In metabolic subtypes such as steatotic HCC, the immune landscape is similarly characterized by T-cell exhaustion, infiltration of M2-like macrophages, and dense stromal content, yet paradoxically, these tumors express high levels of PD-L1, suggesting they may still benefit from ICB therapy [156].

6.1. Spatial Prognostic and Predictive Biomarkers

Several prognostic models incorporate the quantity and spatial distribution of immune cells, including CD8+ T cells [157] and combined T and B cell signatures [158], to predict patient responses to immunotherapies and combination treatments. These spatial metrics serve as powerful biomarkers for patient stratification and outcome prediction.

IMC-based studies comparing proteomic landscapes of primary and recurrent HCCs identified immune features associated with early recurrence. PD-L1+ CD103+ dendritic cells (DCs) were linked to putative interactions between cancer cells undergoing EMT, Tregs, exhausted -cells (Tex), and M2 macrophages, fostering immune evasion [159]. In minimal residual disease (MRD) states, M2-like PDL1+ macrophages interact with CSCs via TGFβ1, contributing to immunosuppression and recurrence. Dual blockade of PD-L1 and TGF-β in animal models restored antitumor activity and eradicated residual CSCs [160].

In addition to individual immune cell subsets, spatially organized immune cell microniches can form both at baseline and in response to immunotherapy. For instance, patients who responded to the combination of cabozantinib and nivolumab exhibited higher densities of tertiary lymphoid aggregates (TLAs), along with increased infiltration of CD3+/CD8+ T cells and CD20+ B cells [161]. These structural immune features were accompanied by upregulation of immune-related genes such as CCL19, CXCL14, IGHM, and CXCL6, indicating an active immune environment [162]. Moreover, TLS density at the time of surgery following neoadjuvant treatment with this combination therapy was positively associated with relapse-free survival [53].

6.2. Emerging Biomarkers for Dynamic TME Monitoring

Noninvasive biomarkers such as exosomal non-coding RNAs and circulating tumor DNA (ctDNA) are emerging as valuable tools for real-time monitoring of disease progression and immunotherapy (IO) efficacy. These biospecimens encompass analytes

originating from malignant cells and diverse non-malignant components within the tumor milieu, including immune infiltrates, stromal fibroblasts, and endothelial elements. Consequently, they provide a dynamic and integrative profile of microenvironmental activity, capturing both tumor-intrinsic alterations and context-dependent responses to therapeutic intervention.

In the INSPIRE trial, ctDNA clearance strongly correlated with durable responses to immune checkpoint inhibitors (ICIs) in patients with castration-resistant prostate cancer. In contrast, in HCC, lower pre-treatment ctDNA levels were linked to a higher likelihood of radiographic complete response [41]. Additionally, multi-omics platforms like the TIMER-HCC score integrate genomic, immune, and stromal features to stratify patients by the predicted response to targeted or immunotherapies [163,164]. This score combines transcriptomic, proteomic, and single-cell RNA sequencing data to map the immune landscape and molecular subtypes of HCC, enabling the identification of biomarkers and immune infiltration patterns associated with therapeutic outcomes [165].

Emerging tools such as spatial technologies and noninvasive biomarkers are transforming our ability to dissect the complex biology of HCC. When combined with artificial intelligence (AI)-driven analytical frameworks, these technologies can uncover hidden patterns within high-dimensional data, offering new insights into tumor heterogeneity, immune evasion, and microenvironmental dynamics. This integrative approach supports the development of more precise and individualized therapies, with the potential to significantly improve outcomes in this challenging malignancy.

7. Challenges and Future Directions

Hepatocellular carcinoma remains a formidable challenge, in large part due to its intrinsic cellular heterogeneity and diverse mechanisms of resistance to TME-directed therapies. Hypoxic niches within the tumor microenvironment foster immunosuppression, promote angiogenesis, and shield malignant cells from immune surveillance and attack. These distinct regions, characterized by oxygen deprivation and metabolic stress, can compromise the effectiveness of systemic therapies, including immune checkpoint inhibitors and antiangiogenic agents. Moreover, the dynamic interplay among stromal, immune, and tumor cells evolves during treatment, creating a complex ecosystem that further complicates therapeutic targeting. Looking ahead, the future of HCC treatment appears increasingly promising as researchers explore novel therapeutic targets and emerging technologies to overcome the complexity of the TME. For instance, targeting specific immune cells, such as CCR8$^+$ Tregs or MARCO$^+$ macrophages, could help dismantle immunosuppressive networks that allow tumors to evade the immune system [166,167]. At the same time, the inhibition of HIF-2α may offer a direct approach to disrupt the hypoxia-driven resistance that undermines current antiangiogenesis therapies.

At the same time, innovations in experimental models and digital technologies are reshaping both preclinical and clinical research. Artificial intelligence (AI)-driven analyses integrating histopathology with multi-omics data are being developed to identify therapeutic vulnerabilities and optimize combination treatments [168,169]. The convergence of novel therapeutic targets, advanced modeling systems, and computational tools opens the door to more effective strategies that may overcome current treatment limitations. For instance, pairing immune checkpoint inhibitors with agents that normalize tumor vasculature, such as bevacizumab, may improve immune cell infiltration while reducing hypoxia-related resistance. In addition, a dual-targeting strategy that addresses both immune evasion and hypoxia pathways could work synergistically to restore antitumor immunity in resistant tumor regions. Together, these emerging approaches offer promise for precision medicine

in hepatocellular carcinoma, potentially transforming this challenging disease into a more manageable condition.

The future of HCC therapy lies in spatially informed, multi-target approaches that address the complexity of the TME. Strategies such as dual checkpoint blockade (e.g., anti-PD-1 + anti-CTLA-4) coupled with hypoxia-targeting agents may overcome spatially driven resistance. Meanwhile, liquid biopsy biomarkers, including circulating tumor DNA (ctDNA) and exosomal RNAs, offer noninvasive tools for real-time monitoring of treatment responses and disease evolution. Artificial intelligence-based analytics and multiomics platforms, such as the TIMER HCC score, enable more precise patient stratification and identification of therapeutic vulnerabilities. By integrating these technological and biological advances, the field is moving closer to transforming HCC from a deadly disease into a controllable and manageable chronic condition.

References

1. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263. [CrossRef] [PubMed]

2. Llovet, J.M.; Kelley, R.K.; Villanueva, A.; Singal, A.G.; Pikarsky, E.; Roayaie, S.; Lencioni, R.; Koike, K.; Zucman-Rossi, J.; Finn, R.S. Hepatocellular carcinoma. *Nat. Rev. Dis. Primers* **2021**, *7*, 6. [CrossRef] [PubMed]

3. Singal, A.G.; Kanwal, F.; Llovet, J.M. Global trends in hepatocellular carcinoma epidemiology: Implications for screening, prevention and therapy. *Nat. Rev. Clin. Oncol.* **2023**, *20*, 864–884. [CrossRef] [PubMed]

4. Lee, Y.T.; Wang, J.J.; Luu, M.; Noureddin, M.; Kosari, K.; Agopian, V.G.; Rich, N.E.; Lu, S.C.; Tseng, H.R.; Nissen, N.N.; et al. The Mortality and Overall Survival Trends of Primary Liver Cancer in the United States. *J. Natl. Cancer Inst.* **2021**, *113*, 1531–1541. [CrossRef] [PubMed]

5. Han, J.; Wang, B.; Liu, W.; Wang, S.; Chen, R.; Chen, M.; Fu, Z. Declining disease burden of HCC in the United States, 1992–2017: A population-based analysis. *Hepatology* **2022**, *76*, 576–588. [CrossRef]

6. Armandi, A.; Rosso, C.; Caviglia, G.P.; Bugianesi, E. An updated overview on hepatocellular carcinoma in patients with Metabolic dysfunction-Associated Steatotic Liver Disease: Trends, pathophysiology and risk-based surveillance. *Metabolism* **2025**, *162*, 156080. [CrossRef]

7. Danpanichkul, P.; Suparan, K.; Sukphutanan, B.; Kaeosri, C.; Tothanarungroj, P.; Sirimangklanurak, S.; Kalligeros, M.; Polpichai, N.; Pang, Y.; Wijarnpreecha, K.; et al. Changes in the epidemiological trends of primary liver cancer in the Asia-Pacific region. *Sci. Rep.* **2024**, *14*, 19544. [CrossRef]

8. Yip, T.C.; Lee, H.W.; Chan, W.K.; Wong, G.L.; Wong, V.W. Asian perspective on NAFLD-associated HCC. *J. Hepatol.* **2022**, *76*, 726–734. [CrossRef]

9. Golabi, P.; Paik, J.M.; AlQahtani, S.; Younossi, Y.; Tuncer, G.; Younossi, Z.M. Burden of non-alcoholic fatty liver disease in Asia, the Middle East and North Africa: Data from Global Burden of Disease 2009–2019. *J. Hepatol.* **2021**, *75*, 795–809. [CrossRef]

10. Le, P.; Tatar, M.; Dasarathy, S.; Alkhouri, N.; Herman, W.H.; Taksler, G.B.; Deshpande, A.; Ye, W.; Adekunle, O.A.; McCullough, A.; et al. Estimated Burden of Metabolic Dysfunction-Associated Steatotic Liver Disease in US Adults, 2020 to 2050. *JAMA Netw. Open* **2025**, *8*, e2454707. [CrossRef]

11. Rinella, M.E.; Neuschwander-Tetri, B.A.; Siddiqui, M.S.; Abdelmalek, M.F.; Caldwell, S.; Barb, D.; Kleiner, D.E.; Loomba, R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* **2023**, *77*, 1797–1835. [CrossRef] [PubMed]

12. Qiu, S.; Cai, J.; Yang, Z.; He, X.; Xing, Z.; Zu, J.; Xie, E.; Henry, L.; Chong, C.R.; John, E.M.; et al. Trends in Hepatocellular Carcinoma Mortality Rates in the US and Projections Through 2040. *JAMA Netw. Open* **2024**, *7*, e2445525. [CrossRef] [PubMed]

13. Singal, A.G.; Llovet, J.M.; Yarchoan, M.; Mehta, N.; Heimbach, J.K.; Dawson, L.A.; Jou, J.H.; Kulik, L.M.; Agopian, V.G.; Marrero, J.A.; et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* **2023**, *78*, 1922–1965. [CrossRef]

14. Villanueva, A. Hepatocellular Carcinoma. *N. Engl. J. Med.* **2019**, *380*, 1450–1462. [CrossRef]

15. Alvarez, C.S.; Petrick, J.L.; Parisi, D.; McMahon, B.J.; Graubard, B.I.; McGlynn, K.A. Racial/ethnic disparities in hepatocellular carcinoma incidence and mortality rates in the United States, 1992–2018. *Hepatology* **2022**, *76*, 589–598. [CrossRef]

16. Filho, A.M.; Laversanne, M.; Ferlay, J.; Colombet, M.; Pineros, M.; Znaor, A.; Parkin, D.M.; Soerjomataram, I.; Bray, F. The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. *Int. J. Cancer* **2025**, *156*, 1336–1346. [CrossRef] [PubMed]

17. Filliol, A.; Saito, Y.; Nair, A.; Dapito, D.H.; Yu, L.X.; Ravichandra, A.; Bhattacharjee, S.; Affo, S.; Fujiwara, N.; Su, H.; et al. Opposing roles of hepatic stellate cell subpopulations in hepatocarcinogenesis. *Nature* **2022**, *610*, 356–365. [CrossRef]

18. Matsuda, M.; Seki, E. Hepatic Stellate Cell-Macrophage Crosstalk in Liver Fibrosis and Carcinogenesis. *Semin. Liver Dis.* **2020**, *40*, 307–320. [CrossRef]

19. Yahoo, N.; Dudek, M.; Knolle, P.; Heikenwalder, M. Role of immune responses in the development of NAFLD-associated liver cancer and prospects for therapeutic modulation. *J. Hepatol.* **2023**, *79*, 538–551. [CrossRef]

20. Galasso, L.; Cerrito, L.; Maccauro, V.; Termite, F.; Mignini, I.; Esposto, G.; Borriello, R.; Ainora, M.E.; Gasbarrini, A.; Zocco, M.A. Inflammatory Response in the Pathogenesis and Treatment of Hepatocellular Carcinoma: A Double-Edged Weapon. *Int. J. Mol. Sci.* **2024**, *25*, 7191. [CrossRef]

21. Jain, R.K. Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. *Cancer Cell* **2014**, *26*, 605–622. [CrossRef] [PubMed]

22. Kremer, K.N.; Khammash, H.A.; Miranda, A.M.; Rutt, L.N.; Twardy, S.M.; Anton, P.E.; Campbell, M.L.; Garza-Ortiz, C.; Orlicky, D.J.; Pelanda, R.; et al. Liver sinusoidal endothelial cells regulate the balance between hepatic immunosuppression and immunosurveillance. *Front. Immunol.* **2024**, *15*, 1497788. [CrossRef]

23. Song, M.; He, J.; Pan, Q.Z.; Yang, J.; Zhao, J.; Zhang, Y.J.; Huang, Y.; Tang, Y.; Wang, Q.; He, J.; et al. Cancer-Associated Fibroblast-Mediated Cellular Crosstalk Supports Hepatocellular Carcinoma Progression. *Hepatology* **2021**, *73*, 1717–1735. [CrossRef] [PubMed]

24. Wang, H.; Liang, Y.; Liu, Z.; Zhang, R.; Chao, J.; Wang, M.; Liu, M.; Qiao, L.; Xuan, Z.; Zhao, H.; et al. POSTN(+) cancer-associated fibroblasts determine the efficacy of immunotherapy in hepatocellular carcinoma. *J. Immunother. Cancer* **2024**, *12*, e008721. [CrossRef] [PubMed]

25. Liu, H.; Wang, M.; Jin, Z.; Sun, D.; Zhu, T.; Liu, X.; Tan, X.; Shi, G. FNDC5 induces M2 macrophage polarization and promotes hepatocellular carcinoma cell growth by affecting the PPARgamma/NF-kappaB/NLRP3 pathway. *Biochem. Biophys. Res. Commun.* **2021**, *582*, 77–85. [CrossRef]

26. Chi, H.C.; Lin, Y.H.; Wu, Y.H.; Chang, C.C.; Wu, C.H.; Yeh, C.T.; Hsieh, C.C.; Lin, K.H. CCL16 is a pro-tumor chemokine that recruits monocytes and macrophages to promote hepatocellular carcinoma progression. *Am. J. Cancer Res.* **2024**, *14*, 3600–3613. [CrossRef]

27. Zhou, J.; Liu, L.; Hu, X.; Feng, R.; Zhao, N.; Zhang, L.; Hu, W.; Zhang, J.; Huang, S.; Liu, L.; et al. Matrix metalloproteinase-21 promotes metastasis via increasing the recruitment and M2 polarization of macrophages in HCC. *Cancer Sci.* **2023**, *114*, 423–435. [CrossRef]

28. Sattiraju, A.; Kang, S.; Giotti, B.; Chen, Z.; Marallano, V.J.; Brusco, C.; Ramakrishnan, A.; Shen, L.; Tsankov, A.M.; Hambardzumyan, D.; et al. Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression. *Immunity* **2023**, *56*, 1825–1843.e6. [CrossRef]

29. Bai, R.; Li, Y.; Jian, L.; Yang, Y.; Zhao, L.; Wei, M. The hypoxia-driven crosstalk between tumor and tumor-associated macrophages: Mechanisms and clinical treatment strategies. *Mol. Cancer* **2022**, *21*, 177. [CrossRef]

30. Zhang, Y.; Pan, Q.; Shao, Z. Extracellular vesicles derived from cancer-associated fibroblasts carry tumor-promotive microRNA-1228-3p to enhance the resistance of hepatocellular carcinoma cells to sorafenib. *Hum. Cell* **2023**, *36*, 296–311. [CrossRef]

31. Qi, Y.; Wang, H.; Zhang, Q.; Liu, Z.; Wang, T.; Wu, Z.; Wu, W. CAF-Released Exosomal miR-20a-5p Facilitates HCC Progression via the LIMA1-Mediated beta-Catenin Pathway. *Cells* **2022**, *11*, 3857. [CrossRef]

32. Eun, J.W.; Yoon, J.H.; Ahn, H.R.; Kim, S.; Kim, Y.B.; Lim, S.B.; Park, W.; Kang, T.W.; Baek, G.O.; Yoon, M.G.; et al. Cancer-associated fibroblast-derived secreted phosphoprotein 1 contributes to resistance of hepatocellular carcinoma to sorafenib and lenvatinib. *Cancer Commun.* **2023**, *43*, 455–479. [CrossRef] [PubMed]

33. Zhao, J.; Lin, E.; Bai, Z.; Jia, Y.; Wang, B.; Dai, Y.; Zhuo, W.; Zeng, G.; Liu, X.; Cai, C.; et al. Cancer-associated fibroblasts induce sorafenib resistance of hepatocellular carcinoma cells through CXCL12/FOLR1. *BMC Cancer* **2023**, *23*, 1198. [CrossRef]

34. Calitz, C.; Rosenquist, J.; Degerstedt, O.; Khaled, J.; Kopsida, M.; Fryknas, M.; Lennernas, H.; Samanta, A.; Heindryckx, F. Influence of extracellular matrix composition on tumour cell behaviour in a biomimetic in vitro model for hepatocellular carcinoma. *Sci. Rep.* **2023**, *13*, 748. [CrossRef] [PubMed]

35. Yuan, Z.; Li, Y.; Zhang, S.; Wang, X.; Dou, H.; Yu, X.; Zhang, Z.; Yang, S.; Xiao, M. Extracellular matrix remodeling in tumor progression and immune escape: From mechanisms to treatments. *Mol. Cancer* **2023**, *22*, 48. [CrossRef]

36. Hu, N.; Li, H.; Tao, C.; Xiao, T.; Rong, W. The Role of Metabolic Reprogramming in the Tumor Immune Microenvironment: Mechanisms and Opportunities for Immunotherapy in Hepatocellular Carcinoma. *Int. J. Mol. Sci.* **2024**, *25*, 5584. [CrossRef]

37. Desert, R.; Chen, W.; Ge, X.; Viel, R.; Han, H.; Athavale, D.; Das, S.; Song, Z.; Lantvit, D.; Cano, L.; et al. Hepatocellular carcinomas, exhibiting intratumor fibrosis, express cancer-specific extracellular matrix remodeling and WNT/TGFB signatures, associated with poor outcome. *Hepatology* **2023**, *78*, 741–757. [CrossRef] [PubMed]

38. Chen, C.; Wang, Z.; Ding, Y.; Qin, Y. Tumor microenvironment-mediated immune evasion in hepatocellular carcinoma. *Front. Immunol.* **2023**, *14*, 1133308. [CrossRef]

39. Siddhartha, R.; Garg, M. Interplay Between Extracellular Matrix Remodeling and Angiogenesis in Tumor Ecosystem. *Mol. Cancer Ther.* **2023**, *22*, 291–305. [CrossRef]

40. Ge, J.; Jiang, H.; Chen, J.; Chen, X.; Zhang, Y.; Shi, L.; Zheng, X.; Jiang, J.; Chen, L. TGF-beta signaling orchestrates cancer-associated fibroblasts in the tumor microenvironment of human hepatocellular carcinoma: Unveiling insights and clinical significance. *BMC Cancer* **2025**, *25*, 113. [CrossRef]

41. Granito, A.; Muratori, L.; Lalanne, C.; Quarneti, C.; Ferri, S.; Guidi, M.; Lenzi, M.; Muratori, P. Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment. *World J. Gastroenterol.* **2021**, *27*, 2994–3009. [CrossRef]

42. You, M.; Gao, Y.; Fu, J.; Xie, R.; Zhu, Z.; Hong, Z.; Meng, L.; Du, S.; Liu, J.; Wang, F.S.; et al. Epigenetic regulation of HBV-specific tumor-infiltrating T cells in HBV-related HCC. *Hepatology* **2023**, *78*, 943–958. [CrossRef] [PubMed]

43. Nasir, N.J.M.; Chuah, S.; Shuen, T.; Prawira, A.; Ba, R.; Lim, M.C.; Chua, J.; Nguyen, P.H.D.; Lim, C.J.; Wasser, M.; et al. GATA4 downregulation enhances CCL20-mediated immunosuppression in hepatocellular carcinoma. *Hepatol. Commun.* **2024**, *8*, e0508. [CrossRef]

44. Luo, X.; Huang, W.; Li, S.; Sun, M.; Hu, D.; Jiang, J.; Zhang, Z.; Wang, Y.; Wang, Y.; Zhang, J.; et al. SOX12 Facilitates Hepatocellular Carcinoma Progression and Metastasis through Promoting Regulatory T-Cells Infiltration and Immunosuppression. *Adv. Sci.* **2024**, *11*, e2310304. [CrossRef] [PubMed]

45. Chen, Y.Y.; Jeffery, H.C.; Hunter, S.; Bhogal, R.; Birtwistle, J.; Braitch, M.K.; Roberts, S.; Ming, M.; Hannah, J.; Thomas, C.; et al. Human intrahepatic regulatory T cells are functional, require IL-2 from effector cells for survival, and are susceptible to Fas ligand-mediated apoptosis. *Hepatology* **2016**, *64*, 138–150. [CrossRef]

46. Guo, C.L.; Yang, X.H.; Cheng, W.; Xu, Y.; Li, J.B.; Sun, Y.X.; Bi, Y.M.; Zhang, L.; Wang, Q.C. Expression of Fas/FasL in CD8+ T and CD3+ Foxp3+ Treg cells--relationship with apoptosis of circulating CD8+ T cells in hepatocellular carcinoma patients. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 2613–2618. [CrossRef]

47. Zhuo, B.; Zhang, Q.; Xie, T.; Wang, Y.; Chen, Z.; Zuo, D.; Guo, B. Integrative epigenetic analysis reveals AP-1 promotes activation of tumor-infiltrating regulatory T cells in HCC. *Cell. Mol. Life Sci.* **2023**, *80*, 103. [CrossRef] [PubMed]

48. Yu, S.; Wang, Y.; Hou, J.; Li, W.; Wang, X.; Xiang, L.; Tan, D.; Wang, W.; Jiang, L.; Claret, F.X.; et al. Tumor-infiltrating immune cells in hepatocellular carcinoma: Tregs is correlated with poor overall survival. *PLoS ONE* **2020**, *15*, e0231003. [CrossRef]

49. Shen, Y.; Wang, H.; Ma, Z.; Hao, M.; Wang, S.; Li, J.; Fang, Y.; Yu, L.; Huang, Y.; Wang, C.; et al. Sorafenib Promotes Treg Cell Differentiation To Compromise Its Efficacy via VEGFR/AKT/Foxo1 Signaling in Hepatocellular Carcinoma. *Cell. Mol. Gastroenterol. Hepatol.* **2025**, *19*, 101454. [CrossRef]

50. Gao, Y.; You, M.; Fu, J.; Tian, M.; Zhong, X.; Du, C.; Hong, Z.; Zhu, Z.; Liu, J.; Markowitz, G.J.; et al. Intratumoral stem-like CCR4+ regulatory T cells orchestrate the immunosuppressive microenvironment in HCC associated with hepatitis B. *J. Hepatol.* **2022**, *76*, 148–159. [CrossRef]

51. Khanam, A.; Ghosh, A.; Chua, J.V.; Kottilil, S. Blockade of CCR4 breaks immune tolerance in chronic hepatitis B patients by modulating regulatory pathways. *J. Transl. Med.* **2023**, *21*, 271. [CrossRef]

52. Liang, Y.; Qiao, L.; Qian, Q.; Zhang, R.; Li, Y.; Xu, X.; Xu, Z.; Bu, Q.; Wang, H.; Li, X.; et al. Integrated single-cell and spatial transcriptomic profiling reveals that CD177(+) Tregs enhance immunosuppression through apoptosis and resistance to immunotherapy in hepatocellular carcinoma. *Oncogene* **2025**, *44*, 1578–1591. [CrossRef]

53. Shu, D.H.; Ho, W.J.; Kagohara, L.T.; Girgis, A.; Shin, S.M.; Danilova, L.; Lee, J.W.; Sidiropoulos, D.N.; Mitchell, S.; Munjal, K.; et al. Immunotherapy response induces divergent tertiary lymphoid structure morphologies in hepatocellular carcinoma. *Nat. Immunol.* **2024**, *25*, 2110–2123. [CrossRef] [PubMed]

54. Teillaud, J.L.; Houel, A.; Panouillot, M.; Riffard, C.; Dieu-Nosjean, M.C. Tertiary lymphoid structures in anticancer immunity. *Nat. Rev. Cancer* **2024**, *24*, 629–646. [CrossRef]

55. Li, J.; Nie, Y.; Jia, W.; Wu, W.; Song, W.; Li, Y. Effect of Tertiary Lymphoid Structures on Prognosis of Patients with Hepatocellular Carcinoma and Preliminary Exploration of Its Formation Mechanism. *Cancers* **2022**, *14*, 5157. [CrossRef] [PubMed]

56. Fan, G.; Gao, R.; Xie, T.; Li, L.; Tang, L.; Han, X.; Shi, Y. DKK1+ tumor cells inhibited the infiltration of CCL19+ fibroblasts and plasma cells contributing to worse immunotherapy response in hepatocellular carcinoma. *Cell Death Dis.* **2024**, *15*, 797. [CrossRef]

57. Wei, Y.; Lao, X.M.; Xiao, X.; Wang, X.Y.; Wu, Z.J.; Zeng, Q.H.; Wu, C.Y.; Wu, R.Q.; Chen, Z.X.; Zheng, L.; et al. Plasma Cell Polarization to the Immunoglobulin G Phenotype in Hepatocellular Carcinomas Involves Epigenetic Alterations and Promotes Hepatoma Progression in Mice. *Gastroenterology* **2019**, *156*, 1890–1904.e16. [CrossRef] [PubMed]

58. Augustin, H.G.; Koh, G.Y. Antiangiogenesis: Vessel Regression, Vessel Normalization, or Both? *Cancer Res.* **2022**, *82*, 15–17. [CrossRef]

59. Vucur, M.; Ghallab, A.; Schneider, A.T.; Adili, A.; Cheng, M.; Castoldi, M.; Singer, M.T.; Buttner, V.; Keysberg, L.S.; Kusgens, L.; et al. Sublethal necroptosis signaling promotes inflammation and liver cancer. *Immunity* **2023**, *56*, 1578–1595.e8. [CrossRef]

60. Mohammed, S.; Thadathil, N.; Selvarani, R.; Nicklas, E.H.; Wang, D.; Miller, B.F.; Richardson, A.; Deepa, S.S. Necroptosis contributes to chronic inflammation and fibrosis in aging liver. *Aging Cell* **2021**, *20*, e13512. [CrossRef]

61. Sin, S.Q.; Mohan, C.D.; Goh, R.M.W.; You, M.; Nayak, S.C.; Chen, L.; Sethi, G.; Rangappa, K.S.; Wang, L. Hypoxia signaling in hepatocellular carcinoma: Challenges and therapeutic opportunities. *Cancer Metastasis Rev.* **2023**, *42*, 741–764. [CrossRef] [PubMed]

62. Chen, S.; Morine, Y.; Tokuda, K.; Yamada, S.; Saito, Y.; Nishi, M.; Ikemoto, T.; Shimada, M. Cancer-associated fibroblast-induced M2-polarized macrophages promote hepatocellular carcinoma progression via the plasminogen activator inhibitor-1 pathway. *Int. J. Oncol.* **2021**, *59*, 59. [CrossRef]

63. Cheng, S.L.; Wu, C.H.; Tsai, Y.J.; Song, J.S.; Chen, H.M.; Yeh, T.K.; Shen, C.T.; Chiang, J.C.; Lee, H.M.; Huang, K.W.; et al. CXCR4 antagonist-loaded nanoparticles reprogram the tumor microenvironment and enhance immunotherapy in hepatocellular carcinoma. *J. Control. Release* **2025**, *379*, 967–981. [CrossRef] [PubMed]

64. Pascut, D.; Pratama, M.Y.; Vo, N.V.T.; Masadah, R.; Tiribelli, C. The Crosstalk between Tumor Cells and the Microenvironment in Hepatocellular Carcinoma: The Role of Exosomal microRNAs and their Clinical Implications. *Cancers* **2020**, *12*, 823. [CrossRef]

65. Wu, Q.; Zhou, L.; Lv, D.; Zhu, X.; Tang, H. Exosome-mediated communication in the tumor microenvironment contributes to hepatocellular carcinoma development and progression. *J. Hematol. Oncol.* **2019**, *12*, 53. [CrossRef]

66. Xu, W.; Cheng, Y.; Guo, Y.; Yao, W.; Qian, H. Targeting tumor associated macrophages in hepatocellular carcinoma. *Biochem. Pharmacol.* **2022**, *199*, 114990. [CrossRef] [PubMed]

67. Li, D.; Zhang, T.; Guo, Y.; Bi, C.; Liu, M.; Wang, G. Biological impact and therapeutic implication of tumor-associated macrophages in hepatocellular carcinoma. *Cell Death Dis.* **2024**, *15*, 498. [CrossRef]

68. Rohrle, N.; Knott, M.M.L.; Anz, D. CCL22 Signaling in the Tumor Environment. *Adv. Exp. Med. Biol.* **2020**, *1231*, 79–96. [CrossRef]

69. Weiss, J.M.; Subleski, J.J.; Back, T.; Chen, X.; Watkins, S.K.; Yagita, H.; Sayers, T.J.; Murphy, W.J.; Wiltrout, R.H. Regulatory T cells and myeloid-derived suppressor cells in the tumor microenvironment undergo Fas-dependent cell death during IL-2/alphaCD40 therapy. *J. Immunol.* **2014**, *192*, 5821–5829. [CrossRef]

70. Yao, C.; Wu, S.; Kong, J.; Sun, Y.; Bai, Y.; Zhu, R.; Li, Z.; Sun, W.; Zheng, L. Angiogenesis in hepatocellular carcinoma: Mechanisms and anti-angiogenic therapies. *Cancer Biol. Med.* **2023**, *20*, 25–43. [CrossRef]

71. Carmeliet, P.; Jain, R.K. Molecular mechanisms and clinical applications of angiogenesis. *Nature* **2011**, *473*, 298–307. [CrossRef] [PubMed]

72. Wen, Y.; Zhou, X.; Lu, M.; He, M.; Tian, Y.; Liu, L.; Wang, M.; Tan, W.; Deng, Y.; Yang, X.; et al. Bclaf1 promotes angiogenesis by regulating HIF-1alpha transcription in hepatocellular carcinoma. *Oncogene* **2019**, *38*, 1845–1859. [CrossRef] [PubMed]

73. von Marschall, Z.; Cramer, T.; Hocker, M.; Finkenzeller, G.; Wiedenmann, B.; Rosewicz, S. Dual mechanism of vascular endothelial growth factor upregulation by hypoxia in human hepatocellular carcinoma. *Gut* **2001**, *48*, 87–96. [CrossRef]

74. Zhang, L.; Xu, J.; Zhou, S.; Yao, F.; Zhang, R.; You, W.; Dai, J.; Yu, K.; Zhang, Y.; Baheti, T.; et al. Endothelial DGKG promotes tumor angiogenesis and immune evasion in hepatocellular carcinoma. *J. Hepatol.* **2024**, *80*, 82–98. [CrossRef]

75. Guo, Y.; Xiao, Z.; Yang, L.; Gao, Y.; Zhu, Q.; Hu, L.; Huang, D.; Xu, Q. Hypoxia-inducible factors in hepatocellular carcinoma (Review). *Oncol. Rep.* **2020**, *43*, 3–15. [CrossRef] [PubMed]

76. Luo, D.; Wang, Z.; Wu, J.; Jiang, C.; Wu, J. The role of hypoxia inducible factor-1 in hepatocellular carcinoma. *BioMed. Res. Int.* **2014**, *2014*, 409272. [CrossRef]

77. Chiu, D.K.; Tse, A.P.; Xu, I.M.; Di Cui, J.; Lai, R.K.; Li, L.L.; Koh, H.Y.; Tsang, F.H.; Wei, L.L.; Wong, C.M.; et al. Hypoxia inducible factor HIF-1 promotes myeloid-derived suppressor cells accumulation through ENTPD2/CD39L1 in hepatocellular carcinoma. *Nat. Commun.* **2017**, *8*, 517. [CrossRef]

78. Chiu, D.K.; Xu, I.M.; Lai, R.K.; Tse, A.P.; Wei, L.L.; Koh, H.Y.; Li, L.L.; Lee, D.; Lo, R.C.; Wong, C.M.; et al. Hypoxia induces myeloid-derived suppressor cell recruitment to hepatocellular carcinoma through chemokine (C-C motif) ligand 26. *Hepatology* **2016**, *64*, 797–813. [CrossRef]

79. Corzo, C.A.; Condamine, T.; Lu, L.; Cotter, M.J.; Youn, J.I.; Cheng, P.; Cho, H.I.; Celis, E.; Quiceno, D.G.; Padhya, T.; et al. HIF-1alpha regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. *J. Exp. Med.* **2010**, *207*, 2439–2453. [CrossRef]

80. Bangoura, G.; Liu, Z.S.; Qian, Q.; Jiang, C.Q.; Yang, G.F.; Jing, S. Prognostic significance of HIF-2alpha/EPAS1 expression in hepatocellular carcinoma. *World J. Gastroenterol.* **2007**, *13*, 3176–3182. [CrossRef]

81. Geis, T.; Doring, C.; Popp, R.; Grossmann, N.; Fleming, I.; Hansmann, M.L.; Dehne, N.; Brune, B. HIF-2alpha-dependent PAI-1 induction contributes to angiogenesis in hepatocellular carcinoma. *Exp. Cell Res.* **2015**, *331*, 46–57. [CrossRef] [PubMed]

82. Sun, H.X.; Xu, Y.; Yang, X.R.; Wang, W.M.; Bai, H.; Shi, R.Y.; Nayar, S.K.; Devbhandari, R.P.; He, Y.Z.; Zhu, Q.F.; et al. Hypoxia inducible factor 2 alpha inhibits hepatocellular carcinoma growth through the transcription factor dimerization partner 3/E2F transcription factor 1-dependent apoptotic pathway. *Hepatology* **2013**, *57*, 1088–1097. [CrossRef]

83. Yang, S.L.; Liu, L.P.; Niu, L.; Sun, Y.F.; Yang, X.R.; Fan, J.; Ren, J.W.; Chen, G.G.; Lai, P.B. Downregulation and pro-apoptotic effect of hypoxia-inducible factor 2 alpha in hepatocellular carcinoma. *Oncotarget* **2016**, *7*, 34571–34581. [CrossRef]

84. Yang, Y.; Chen, W.; Mai, W.; Gao, Y. HIF-2alpha regulates proliferation, invasion, and metastasis of hepatocellular carcinoma cells via VEGF/Notch1 signaling axis after insufficient radiofrequency ablation. *Front. Oncol.* **2022**, *12*, 998295. [CrossRef]

85. Xu, J.; Zheng, L.; Chen, J.; Sun, Y.; Lin, H.; Jin, R.A.; Tang, M.; Liang, X.; Cai, X. Increasing AR by HIF-2alpha inhibitor (PT-2385) overcomes the side-effects of sorafenib by suppressing hepatocellular carcinoma invasion via alteration of pSTAT3, pAKT and pERK signals. *Cell Death Dis.* **2017**, *8*, e3095. [CrossRef] [PubMed]

86. Vanderborght, B.; De Muynck, K.; Lefere, S.; Geerts, A.; Degroote, H.; Verhelst, X.; Van Vlierberghe, H.; Devisscher, L. Effect of isoform-specific HIF-1alpha and HIF-2alpha antisense oligonucleotides on tumorigenesis, inflammation and fibrosis in a hepatocellular carcinoma mouse model. *Oncotarget* **2020**, *11*, 4504–4520. [CrossRef]

87. Shi, Y.; Gilkes, D.M. HIF-1 and HIF-2 in cancer: Structure, regulation, and therapeutic prospects. *Cell. Mol. Life Sci.* **2025**, *82*, 44. [CrossRef] [PubMed]

88. Akkiz, H. Emerging Role of Cancer-Associated Fibroblasts in Progression and Treatment of Hepatocellular Carcinoma. *Int. J. Mol. Sci.* **2023**, *24*, 3941. [CrossRef]

89. Yuan, Y.; Wu, D.; Li, J.; Huang, D.; Zhao, Y.; Gao, T.; Zhuang, Z.; Cui, Y.; Zheng, D.Y.; Tang, Y. Mechanisms of tumor-associated macrophages affecting the progression of hepatocellular carcinoma. *Front. Pharmacol.* **2023**, *14*, 1217400. [CrossRef]

90. Zhang, Z.; Zhang, Q.; Wang, Y. CAF-mediated tumor vascularization: From mechanistic insights to targeted therapies. *Cell Signal* **2025**, *132*, 111827. [CrossRef]

91. Baglieri, J.; Brenner, D.A.; Kisseleva, T. The Role of Fibrosis and Liver-Associated Fibroblasts in the Pathogenesis of Hepatocellular Carcinoma. *Int. J. Mol. Sci.* **2019**, *20*, 1723. [CrossRef] [PubMed]

92. Capece, D.; Fischietti, M.; Verzella, D.; Gaggiano, A.; Cicciarelli, G.; Tessitore, A.; Zazzeroni, F.; Alesse, E. The inflammatory microenvironment in hepatocellular carcinoma: A pivotal role for tumor-associated macrophages. *BioMed. Res. Int.* **2013**, *2013*, 187204. [CrossRef] [PubMed]

93. Fu, L.Q.; Du, W.L.; Cai, M.H.; Yao, J.Y.; Zhao, Y.Y.; Mou, X.Z. The roles of tumor-associated macrophages in tumor angiogenesis and metastasis. *Cell. Immunol.* **2020**, *353*, 104119. [CrossRef]

94. Hosaka, K.; Yang, Y.; Seki, T.; Fischer, C.; Dubey, O.; Fredlund, E.; Hartman, J.; Religa, P.; Morikawa, H.; Ishii, Y.; et al. Pericyte-fibroblast transition promotes tumor growth and metastasis. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E5618–E5627. [CrossRef]

95. Pasquier, J.; Ghiabi, P.; Chouchane, L.; Razzouk, K.; Rafii, S.; Rafii, A. Angiocrine endothelium: From physiology to cancer. *J. Transl. Med.* **2020**, *18*, 52. [CrossRef]

96. Giannelli, G.; Villa, E.; Lahn, M. Transforming growth factor-beta as a therapeutic target in hepatocellular carcinoma. *Cancer Res.* **2014**, *74*, 1890–1894. [CrossRef]

97. Fabregat, I.; Caballero-Diaz, D. Transforming Growth Factor-beta-Induced Cell Plasticity in Liver Fibrosis and Hepatocarcinogenesis. *Front. Oncol.* **2018**, *8*, 357. [CrossRef] [PubMed]

98. Soukupova, J.; Malfettone, A.; Bertran, E.; Hernandez-Alvarez, M.I.; Penuelas-Haro, I.; Dituri, F.; Giannelli, G.; Zorzano, A.; Fabregat, I. Epithelial-Mesenchymal Transition (EMT) Induced by TGF-beta in Hepatocellular Carcinoma Cells Reprograms Lipid Metabolism. *Int. J. Mol. Sci.* **2021**, *22*, 5543. [CrossRef]

99. Malfettone, A.; Soukupova, J.; Bertran, E.; Crosas-Molist, E.; Lastra, R.; Fernando, J.; Koudelkova, P.; Rani, B.; Fabra, A.; Serrano, T.; et al. Transforming growth factor-beta-induced plasticity causes a migratory stemness phenotype in hepatocellular carcinoma. *Cancer Lett.* **2017**, *392*, 39–50. [CrossRef]

100. Paskeh, M.D.A.; Ghadyani, F.; Hashemi, M.; Abbaspour, A.; Zabolian, A.; Javanshir, S.; Razzazan, M.; Mirzaei, S.; Entezari, M.; Goharrizi, M.; et al. Biological impact and therapeutic perspective of targeting PI3K/Akt signaling in hepatocellular carcinoma: Promises and Challenges. *Pharmacol. Res.* **2023**, *187*, 106553. [CrossRef]

101. Ngo, M.T.; Jeng, H.Y.; Kuo, Y.C.; Diony Nanda, J.; Brahmadhi, A.; Ling, T.Y.; Chang, T.S.; Huang, Y.H. The Role of IGF/IGF-1R Signaling in Hepatocellular Carcinomas: Stemness-Related Properties and Drug Resistance. *Int. J. Mol. Sci.* **2021**, *22*, 1931. [CrossRef] [PubMed]

102. Bussolati, B.; Assenzio, B.; Deregibus, M.C.; Camussi, G. The proangiogenic phenotype of human tumor-derived endothelial cells depends on thrombospondin-1 downregulation via phosphatidylinositol 3-kinase/Akt pathway. *J. Mol. Med.* **2006**, *84*, 852–863. [CrossRef] [PubMed]

103. Chen, X.; Chi, H.; Zhao, X.; Pan, R.; Wei, Y.; Han, Y. Role of Exosomes in Immune Microenvironment of Hepatocellular Carcinoma. *J. Oncol.* **2022**, *2022*, 2521025. [CrossRef]

104. Xu, H.Z.; Lin, X.Y.; Xu, Y.X.; Xue, H.B.; Lin, S.; Xu, T.W. An emerging research: The role of hepatocellular carcinoma-derived exosomal circRNAs in the immune microenvironment. *Front. Immunol.* **2023**, *14*, 1227150. [CrossRef]

105. Zhang, Y.; Zhang, C.; Wu, N.; Feng, Y.; Wang, J.; Ma, L.; Chen, Y. The role of exosomes in liver cancer: Comprehensive insights from biological function to therapeutic applications. *Front. Immunol.* **2024**, *15*, 1473030. [CrossRef]

106. Papadakos, S.P.; Machairas, N.; Stergiou, I.E.; Arvanitakis, K.; Germanidis, G.; Frampton, A.E.; Theocharis, S. Unveiling the Yin-Yang Balance of M1 and M2 Macrophages in Hepatocellular Carcinoma: Role of Exosomes in Tumor Microenvironment and Immune Modulation. *Cells* **2023**, *12*, 2036. [CrossRef] [PubMed]

107. Hsu, C.Y.; Ahmed, A.T.; Rab, S.O.; Uthirapathy, S.; Ballal, S.; Kalia, R.; Arya, R.; Nathiya, D.; Kariem, M.; Kadhim, A.J. Cancer-associated fibroblast-derived exosomes in cancer progression: A focus on hepatocellular carcinoma. *Exp. Cell Res.* **2025**, *445*, 114424. [CrossRef]

108. Ge, Y.; Jiang, L.; Dong, Q.; Xu, Y.; Yam, J.W.P.; Zhong, X. Exosome-mediated Crosstalk in the Tumor Immune Microenvironment: Critical Drivers of Hepatocellular Carcinoma Progression. *J. Clin. Transl. Hepatol.* **2025**, *13*, 143–161. [CrossRef]

109. Hu, R.; Jahan, M.S.; Tang, L. ExoPD-L1: An assistant for tumor progression and potential diagnostic marker. *Front. Oncol.* **2023**, *13*, 1194180. [CrossRef]

110. Chen, J.; Lin, Z.; Liu, L.; Zhang, R.; Geng, Y.; Fan, M.; Zhu, W.; Lu, M.; Lu, L.; Jia, H.; et al. GOLM1 exacerbates CD8(+) T cell suppression in hepatocellular carcinoma by promoting exosomal PD-L1 transport into tumor-associated macrophages. *Signal Transduct. Target. Ther.* **2021**, *6*, 397. [CrossRef]

111. Lin, X.; Shao, H.; Tang, Y.; Wang, Q.; Yang, Z.; Wu, H.; Xing, T. High expression of circulating exosomal PD-L1 contributes to immune escape of hepatocellular carcinoma and immune clearance of chronic hepatitis B. *Aging* **2024**, *16*, 11373–11384. [CrossRef] [PubMed]

112. Wang, H.C.; Yin, W.X.; Jiang, M.; Han, J.Y.; Kuai, X.W.; Sun, R.; Sun, Y.F.; Ji, J.L. Function and biomedical implications of exosomal microRNAs delivered by parenchymal and nonparenchymal cells in hepatocellular carcinoma. *World J. Gastroenterol.* **2023**, *29*, 5435–5451. [CrossRef] [PubMed]

113. Han, Y.; Gong, W.S.; Xing, X.S.; Zhou, H.; Wang, X.L.; Xu, Y.; Zhou, X.L.; Xue, W.L. miR-183-5p-enriched extracellular vesicles promote the crosstalk between hepatocellular carcinoma cell and endothelial cell via SIK1/PI3K/AKT and CCL20/CCR6 signaling pathways. *Front. Oncol.* **2025**, *15*, 1532239. [CrossRef] [PubMed]

114. Yang, B.; Feng, X.; Liu, H.; Tong, R.; Wu, J.; Li, C.; Yu, H.; Chen, Y.; Cheng, Q.; Chen, J.; et al. High-metastatic cancer cells derived exosomal miR92a-3p promotes epithelial-mesenchymal transition and metastasis of low-metastatic cancer cells by regulating PTEN/Akt pathway in hepatocellular carcinoma. *Oncogene* **2020**, *39*, 6529–6543. [CrossRef]

115. Abou-Alfa, G.K.; Meyer, T.; Cheng, A.L.; El-Khoueiry, A.B.; Rimassa, L.; Ryoo, B.Y.; Cicin, I.; Merle, P.; Chen, Y.; Park, J.W.; et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N. Engl. J. Med.* **2018**, *379*, 54–63. [CrossRef]

116. Bruix, J.; Qin, S.; Merle, P.; Granito, A.; Huang, Y.H.; Bodoky, G.; Pracht, M.; Yokosuka, O.; Rosmorduc, O.; Breder, V.; et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **2017**, *389*, 56–66. [CrossRef]

117. Zhu, A.X.; Baron, A.D.; Malfertheiner, P.; Kudo, M.; Kawazoe, S.; Pezet, D.; Weissinger, F.; Brandi, G.; Barone, C.A.; Okusaka, T.; et al. Ramucirumab as Second-Line Treatment in Patients With Advanced Hepatocellular Carcinoma: Analysis of REACH Trial Results by Child-Pugh Score. *JAMA Oncol.* **2017**, *3*, 235–243. [CrossRef]

118. Kudo, M.; Finn, R.S.; Qin, S.; Han, K.H.; Ikeda, K.; Piscaglia, F.; Baron, A.; Park, J.W.; Han, G.; Jassem, J.; et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. *Lancet* **2018**, *391*, 1163–1173. [CrossRef]

119. Finn, R.S.; Qin, S.; Ikeda, M.; Galle, P.R.; Ducreux, M.; Kim, T.Y.; Kudo, M.; Breder, V.; Merle, P.; Kaseb, A.O.; et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N. Engl. J. Med.* **2020**, *382*, 1894–1905. [CrossRef]

120. Qin, S.; Chan, S.L.; Gu, S.; Bai, Y.; Ren, Z.; Lin, X.; Chen, Z.; Jia, W.; Jin, Y.; Guo, Y.; et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): A randomised, open-label, international phase 3 study. *Lancet* **2023**, *402*, 1133–1146. [CrossRef]

121. Llovet, J.M.; Kudo, M.; Merle, P.; Meyer, T.; Qin, S.; Ikeda, M.; Xu, R.; Edeline, J.; Ryoo, B.Y.; Ren, Z.; et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): A randomised, double-blind, phase 3 trial. *Lancet Oncol.* **2023**, *24*, 1399–1410. [CrossRef]

122. Kelley, R.K.; Rimassa, L.; Cheng, A.L.; Kaseb, A.; Qin, S.; Zhu, A.X.; Chan, S.L.; Melkadze, T.; Sukeepaisarnjaroen, W.; Breder, V.; et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* **2022**, *23*, 995–1008. [CrossRef] [PubMed]

123. Morita, S.; Kikuchi, H.; Birch, G.; Matsui, A.; Morita, A.; Kobayashi, T.; Ruan, Z.; Huang, P.; Hernandez, A.; Coyne, E.M.; et al. Preventing NK cell activation in the damaged liver induced by cabozantinib/PD-1 blockade increases survival in hepatocellular carcinoma models. *bioRxiv* **2023**. [CrossRef]

124. Abou-Alfa, G.K.; Lau, G.; Kudo, M.; Chan, S.L.; Kelley, R.K.; Furuse, J.; Sukeepaisarnjaroen, W.; Kang, Y.K.; Van Dao, T.; De Toni, E.N.; et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid.* **2022**, *1*, EVIDoa2100070. [CrossRef] [PubMed]

125. Sangro, B.; Chan, S.L.; Kelley, R.K.; Lau, G.; Kudo, M.; Sukeepaisarnjaroen, W.; Yarchoan, M.; De Toni, E.N.; Furuse, J.; Kang, Y.K.; et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *Ann. Oncol.* **2024**, *35*, 448–457. [CrossRef]

126. Yau, T.; Zagonel, V.; Santoro, A.; Acosta-Rivera, M.; Choo, S.P.; Matilla, A.; He, A.R.; Cubillo Gracian, A.; El-Khoueiry, A.B.; Sangro, B.; et al. Nivolumab Plus Cabozantinib With or Without Ipilimumab for Advanced Hepatocellular Carcinoma: Results From Cohort 6 of the CheckMate 040 Trial. *J. Clin. Oncol.* **2023**, *41*, 1747–1757. [CrossRef] [PubMed]

127. Verset, G.; Borbath, I.; Karwal, M.; Verslype, C.; Van Vlierberghe, H.; Kardosh, A.; Zagonel, V.; Stal, P.; Sarker, D.; Palmer, D.H.; et al. Pembrolizumab Monotherapy for Previously Untreated Advanced Hepatocellular Carcinoma: Data from the Open-Label, Phase II KEYNOTE-224 Trial. *Clin. Cancer Res.* **2022**, *28*, 2547–2554. [CrossRef]

128. Borbath, I.; Van Laethem, J.-L.; Karwal, M.; Verslype, C.; Van Vlierberghe, H.; Kardosh, A.; Bergamo, F.; Stål, P.; Sarker, D.; Palmer, D.H.; et al. Pembrolizumab monotherapy for previously untreated advanced hepatocellular carcinoma (aHCC): 3-year follow-up of the phase 2 KEYNOTE-224 study. *J. Clin. Oncol.* **2022**, *40*, 4109. [CrossRef]

129. Van Laethem, J.-L.; Borbath, I.; Karwal, M.; Verslype, C.; Van Vlierberghe, H.; Kardosh, A.; Zagonel, V.; Stal, P.; Sarker, D.; Palmer, D.H.; et al. Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): Phase II KEYNOTE-224 study. *J. Clin. Oncol.* **2021**, *39*, 297. [CrossRef]

130. Finn, R.S.; Ryoo, B.Y.; Merle, P.; Kudo, M.; Bouattour, M.; Lim, H.Y.; Breder, V.; Edeline, J.; Chao, Y.; Ogasawara, S.; et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J. Clin. Oncol.* **2020**, *38*, 193–202. [CrossRef]

131. Merle, P.; Kudo, M.; Edeline, J.; Bouattour, M.; Cheng, A.L.; Chan, S.L.; Yau, T.; Garrido, M.; Knox, J.; Daniele, B.; et al. Pembrolizumab as Second-Line Therapy for Advanced Hepatocellular Carcinoma: Longer Term Follow-Up from the Phase 3 KEYNOTE-240 Trial. *Liver Cancer* **2023**, *12*, 309–320. [CrossRef] [PubMed]

132. Merle, P.; Edeline, J.; Bouattour, M.; Cheng, A.-L.; Chan, S.L.; Yau, T.; Garrido, M.; Knox, J.J.; Daniele, B.; Zhu, A.X.; et al. Pembrolizumab (pembro) vs placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase III KEYNOTE-240 study. *J. Clin. Oncol.* **2021**, *39*, 268. [CrossRef]

133. Xu, D.; Wang, H.; Bao, Q.; Jin, K.; Liu, M.; Liu, W.; Yan, X.; Wang, L.; Zhang, Y.; Wang, G.; et al. The anti-PD-L1/CTLA-4 bispecific antibody KN046 plus lenvatinib in advanced unresectable or metastatic hepatocellular carcinoma: A phase II trial. *Nat. Commun.* **2025**, *16*, 1443. [CrossRef]

134. Clouthier, D.L.; Lien, S.C.; Yang, S.Y.C.; Nguyen, L.T.; Manem, V.S.K.; Gray, D.; Ryczko, M.; Razak, A.R.A.; Lewin, J.; Lheureux, S.; et al. An interim report on the investigator-initiated phase 2 study of pembrolizumab immunological response evaluation (INSPIRE). *J. Immunother. Cancer* **2019**, *7*, 72. [CrossRef]

135. Gordan, J.D.; Kennedy, E.B.; Abou-Alfa, G.K.; Beal, E.; Finn, R.S.; Gade, T.P.; Goff, L.; Gupta, S.; Guy, J.; Hoang, H.T.; et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update. *J. Clin. Oncol.* **2024**, *42*, 1830–1850. [CrossRef]

136. Abou-Alfa, G.K.; Chan, S.L.; Kudo, M.; Lau, G.; Kelley, R.K.; Furuse, J.; Sukeepaisarnjaroen, W.; Kang, Y.-K.; Dao, T.V.; De Toni, E.N.; et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J. Clin. Oncol.* **2022**, *40*, 379. [CrossRef]

137. Finn, R.S.; Qin, S.; Ikeda, M.; Galle, P.R.; Ducreux, M.; Kim, T.-Y.; Lim, H.Y.; Kudo, M.; Breder, V.V.; Merle, P.; et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J. Clin. Oncol.* **2021**, *39*, 267. [CrossRef]

138. Vogel, A.; Chan, S.L.; Ren, Z.; Bai, Y.; Gu, S.; Lin, X.; Chen, Z.; Jia, W.; Jin, Y.; Guo, Y.; et al. Camrelizumab plus rivoceranib vs sorafenib as first-line therapy for unresectable hepatocellular carcinoma (uHCC): Final overall survival analysis of the phase 3 CARES-310 study. *J. Clin. Oncol.* **2024**, *42*, 4110. [CrossRef]

139. Finn, R.S.; Kudo, M.; Merle, P.; Meyer, T.; Qin, S.; Ikeda, M.; Xu, R.; Edeline, J.; Ryoo, B.-Y.; Ren, Z.; et al. Lenvatinib plus pembrolizumab versus lenvatinib alone as first-line therapy for advanced hepatocellular carcinoma: Longer-term efficacy and safety results from the phase 3 LEAP-002 study. *J. Clin. Oncol.* **2024**, *42*, 482. [CrossRef]

140. Vandereyken, K.; Sifrim, A.; Thienpont, B.; Voet, T. Methods and applications for single-cell and spatial multi-omics. *Nat. Rev. Genet.* **2023**, *24*, 494–515. [CrossRef]

141. Palla, G.; Fischer, D.S.; Regev, A.; Theis, F.J. Spatial components of molecular tissue biology. *Nat. Biotechnol.* **2022**, *40*, 308–318. [CrossRef] [PubMed]

142. Ma, L.; Hernandez, M.O.; Zhao, Y.; Mehta, M.; Tran, B.; Kelly, M.; Rae, Z.; Hernandez, J.M.; Davis, J.L.; Martin, S.P.; et al. Tumor Cell Biodiversity Drives Microenvironmental Reprogramming in Liver Cancer. *Cancer Cell* **2019**, *36*, 418–430.e6. [CrossRef] [PubMed]

143. Yang, C.; Zhang, S.; Cheng, Z.; Liu, Z.; Zhang, L.; Jiang, K.; Geng, H.; Qian, R.; Wang, J.; Huang, X.; et al. Multi-region sequencing with spatial information enables accurate heterogeneity estimation and risk stratification in liver cancer. *Genome Med.* **2022**, *14*, 142. [CrossRef] [PubMed]

144. Nguyen, P.H.D.; Ma, S.; Phua, C.Z.J.; Kaya, N.A.; Lai, H.L.H.; Lim, C.J.; Lim, J.Q.; Wasser, M.; Lai, L.; Tam, W.L.; et al. Intratumoural immune heterogeneity as a hallmark of tumour evolution and progression in hepatocellular carcinoma. *Nat. Commun.* **2021**, *12*, 227. [CrossRef]

145. Jing, S.Y.; Liu, D.; Feng, N.; Dong, H.; Wang, H.Q.; Yan, X.; Chen, X.F.; Qu, M.C.; Lin, P.; Yi, B.; et al. Spatial multiomics reveals a subpopulation of fibroblasts associated with cancer stemness in human hepatocellular carcinoma. *Genome Med.* **2024**, *16*, 98. [CrossRef]

146. Fan, G.; Xie, T.; Li, L.; Tang, L.; Han, X.; Shi, Y. Single-cell and spatial analyses revealed the co-location of cancer stem cells and SPP1+ macrophage in hypoxic region that determines the poor prognosis in hepatocellular carcinoma. *NPJ Precis. Oncol.* **2024**, *8*, 75. [CrossRef]

147. Virtanen, A.S.J.; Huopaniemi, T.; Narhi, M.V.O.; Pertovaara, A.; Wallgren, K. The effect of temporal parameters on subjective sensations evoked by electrical tooth stimulation. *Pain* **1987**, *30*, 361–371. [CrossRef]

148. Liu, Y.; Xun, Z.; Ma, K.; Liang, S.; Li, X.; Zhou, S.; Sun, L.; Liu, Y.; Du, Y.; Guo, X.; et al. Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. *J. Hepatol.* **2023**, *78*, 770–782. [CrossRef]

149. Jin, H.; Kim, W.; Yuan, M.; Li, X.; Yang, H.; Li, M.; Shi, M.; Turkez, H.; Uhlen, M.; Zhang, C.; et al. Identification of SPP1 (+) macrophages as an immune suppressor in hepatocellular carcinoma using single-cell and bulk transcriptomics. *Front. Immunol.* **2024**, *15*, 1446453. [CrossRef]

150. Long, F.; Zhong, W.; Zhao, F.; Xu, Y.; Hu, X.; Jia, G.; Huang, L.; Yi, K.; Wang, N.; Si, H.; et al. DAB2 (+) macrophages support FAP (+) fibroblasts in shaping tumor barrier and inducing poor clinical outcomes in liver cancer. *Theranostics* **2024**, *14*, 4822–4843. [CrossRef]

151. Li, Y.; Li, F.; Xu, L.; Shi, X.; Xue, H.; Liu, J.; Bai, S.; Wu, Y.; Yang, Z.; Xue, F.; et al. Single cell analyses reveal the PD-1 blockade response-related immune features in hepatocellular carcinoma. *Theranostics* **2024**, *14*, 3526–3547. [CrossRef] [PubMed]

152. Ning, J.; Ye, Y.; Shen, H.; Zhang, R.; Li, H.; Song, T.; Zhang, R.; Liu, P.; Chen, G.; Wang, H.; et al. Macrophage-coated tumor cluster aggravates hepatoma invasion and immunotherapy resistance via generating local immune deprivation. *Cell Rep. Med.* **2024**, *5*, 101505. [CrossRef] [PubMed]

153. Qiu, X.; Zhou, T.; Li, S.; Wu, J.; Tang, J.; Ma, G.; Yang, S.; Hu, J.; Wang, K.; Shen, S.; et al. Spatial single-cell protein landscape reveals vimentin(high) macrophages as immune-suppressive in the microenvironment of hepatocellular carcinoma. *Nat. Cancer* **2024**, *5*, 1557–1578. [CrossRef] [PubMed]

154. Sharma, A.; Seow, J.J.W.; Dutertre, C.A.; Pai, R.; Bleriot, C.; Mishra, A.; Wong, R.M.M.; Singh, G.S.N.; Sudhagar, S.; Khalilnezhad, S.; et al. Onco-fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma. *Cell* **2020**, *183*, 377–394.e21. [CrossRef]

155. Li, Z.; Pai, R.; Gupta, S.; Currenti, J.; Guo, W.; Di Bartolomeo, A.; Feng, H.; Zhang, Z.; Li, Z.; Liu, L.; et al. Presence of onco-fetal neighborhoods in hepatocellular carcinoma is associated with relapse and response to immunotherapy. *Nat. Cancer* **2024**, *5*, 167–186. [CrossRef]

156. Murai, H.; Kodama, T.; Maesaka, K.; Tange, S.; Motooka, D.; Suzuki, Y.; Shigematsu, Y.; Inamura, K.; Mise, Y.; Saiura, A.; et al. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. *Hepatology* **2023**, *77*, 77–91. [CrossRef]

157. Salie, H.; Wischer, L.; D'Alessio, A.; Godbole, I.; Suo, Y.; Otto-Mora, P.; Beck, J.; Neumann, O.; Stenzinger, A.; Schirmacher, P.; et al. Spatial single-cell profiling and neighbourhood analysis reveal the determinants of immune architecture connected to checkpoint inhibitor therapy outcome in hepatocellular carcinoma. *Gut* **2025**, *74*, 451–466. [CrossRef]

158. Kurebayashi, Y.; Sugimoto, K.; Tsujikawa, H.; Matsuda, K.; Nomura, R.; Ueno, A.; Masugi, Y.; Yamazaki, K.; Effendi, K.; Takeuchi, H.; et al. Spatial Dynamics of T- and B-Cell Responses Predicts Clinical Outcome of Resectable and Unresectable Hepatocellular Carcinoma. *Clin. Cancer Res.* **2024**, *30*, 5666–5680. [CrossRef]

159. Yang, M.; Song, X.; Zhang, F.; Li, M.; Chang, W.; Wang, Z.; Li, M.; Shan, H.; Li, D. Spatial proteomic landscape of primary and relapsed hepatocellular carcinoma reveals immune escape characteristics in early relapse. *Hepatology* **2025**, *81*, 1452–1467. [CrossRef]

160. Lemaitre, L.; Adeniji, N.; Suresh, A.; Reguram, R.; Zhang, J.; Park, J.; Reddy, A.; Trevino, A.E.; Mayer, A.T.; Deutzmann, A.; et al. Spatial analysis reveals targetable macrophage-mediated mechanisms of immune evasion in hepatocellular carcinoma minimal residual disease. *Nat. Cancer* **2024**, *5*, 1534–1556. [CrossRef]

161. Ho, W.J.; Zhu, Q.; Durham, J.; Popovic, A.; Xavier, S.; Leatherman, J.; Mohan, A.; Mo, G.; Zhang, S.; Gross, N.; et al. Neoadjuvant Cabozantinib and Nivolumab Converts Locally Advanced HCC into Resectable Disease with Enhanced Antitumor Immunity. *Nat. Cancer* **2021**, *2*, 891–903. [CrossRef] [PubMed]

162. Zhang, S.; Yuan, L.; Danilova, L.; Mo, G.; Zhu, Q.; Deshpande, A.; Bell, A.T.F.; Elisseeff, J.; Popel, A.S.; Anders, R.A.; et al. Spatial transcriptomics analysis of neoadjuvant cabozantinib and nivolumab in advanced hepatocellular carcinoma identifies independent mechanisms of resistance and recurrence. *Genome Med.* **2023**, *15*, 72. [CrossRef]

163. Chen, Y.; Deng, X.; Li, Y.; Han, Y.; Peng, Y.; Wu, W.; Wang, X.; Ma, J.; Hu, E.; Zhou, X.; et al. Comprehensive molecular classification predicted microenvironment profiles and therapy response for HCC. *Hepatology* **2024**, *80*, 536–551. [CrossRef] [PubMed]

164. Du, J.; Zhang, E.; Huang, Z. The predictive value of next generation sequencing for matching advanced hepatocellular carcinoma patients to targeted and immunotherapy. *Front. Immunol.* **2024**, *15*, 1358306. [CrossRef]

165. Dhanasekaran, R.; Suzuki, H.; Lemaitre, L.; Kubota, N.; Hoshida, Y. Molecular and immune landscape of hepatocellular carcinoma to guide therapeutic decision-making. *Hepatology* **2025**, *81*, 1038–1057. [CrossRef] [PubMed]

166. Ueyama, A.; Nogami, W.; Nashiki, K.; Haruna, M.; Miwa, H.; Hagiwara, M.; Nagira, M.; Wada, H.; Nagira, Y. Immunotherapy Targeting CCR8+ Regulatory T Cells Induces Antitumor Effects via Dramatic Changes to the Intratumor CD8+ T Cell Profile. *J. Immunol.* **2023**, *211*, 673–682. [CrossRef]

167. Ding, L.; Qian, J.; Yu, X.; Wu, Q.; Mao, J.; Liu, X.; Wang, Y.; Guo, D.; Su, R.; Xie, H.; et al. Blocking MARCO(+) tumor-associated macrophages improves anti-PD-L1 therapy of hepatocellular carcinoma by promoting the activation of STING-IFN type I pathway. *Cancer Lett.* **2024**, *582*, 216568. [CrossRef]

168. Zeng, Q.; Klein, C.; Caruso, S.; Maille, P.; Allende, D.S.; Minguez, B.; Iavarone, M.; Ningarhari, M.; Casadei-Gardini, A.; Pedica, F.; et al. Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab-bevacizumab in patients with hepatocellular carcinoma: A multicentre retrospective study. *Lancet Oncol.* **2023**, *24*, 1411–1422. [CrossRef]

169. Chen, B.; Garmire, L.; Calvisi, D.F.; Chua, M.S.; Kelley, R.K.; Chen, X. Harnessing big 'omics' data and AI for drug discovery in hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 238–251. [CrossRef]