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Review

Signaling Pathway Remodeling and Molecular Regulation in the HCC TME: Dynamic Evolution and Clinical Therapeutic Advances

Lin Xu[1,†], Xuanhao Zhang[1,†], Hengzhou Zhu[1], Dong Niu[1], Xiaodan Zhu[1], Chunhui Jin[1,*]

[1]Department of Oncology, Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine, 214071 Wuxi, Jiangsu, China
*Correspondence: wxzy013@njucm.edu.cn (Chunhui Jin)
[†]These authors contributed equally.

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Abstract

The dynamic evolution of signaling pathway remodeling and molecular regulation within the tumor microenvironment (TME) of hepatocellular carcinoma (HCC) play a critical role in the onset and progression of this malignancy. As chronic hepatitis progresses to cirrhosis and ultimately to HCC, the signaling pathways and TME show stage-specific characteristics that provide important insights into the therapeutic challenges and opportunities. In this review, we profiled the principal components of the HCC TME, along with pivotal signaling pathways, including the receptor tyrosine kinase (RTK) and extracellular signal-regulated kinase (ERK) pathways. Furthermore, we characterized the dynamic transformation of the TME from an inflammatory state in the hepatitis phase to a fibrotic state in the cirrhosis phase. Ultimately, we assessed the therapeutic potential of current HCC targets emphasizing emerging strategies for precision and personalized treatment.

Keywords: hepatocellular carcinoma; tumor microenvironment; signal transduction; disease progression; molecular targeted therapy; immunotherapy

1. Introduction

Hepatocellular carcinoma (HCC), the most prevalent primary liver cancer globally, is notorious for an alarmingly high mortality rate. Its epidemiological profile resembles that of chronic liver diseases, with the main etiological factors including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol consumption, and metabolic diseases. In developed countries, the incidence of HCC has kept rising over decades [1]. Additionally, HCC may also arise from non-viral factors, such as metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease [2]. These signals indicate the heavy load that HCC poses on the global public health.

Generally, hepatitis and liver cirrhosis develop sequentially prior to HCC. Firstly, in the hepatitis stage, HBV and HCV infections are significant inducers for HCC. In the case of HBV infection, HBV proteins, such as HBV X protein (HBx), can facilitate the development of HCC by modulating chromatin and dysregulating the expression of tumor suppressor genes [3]. HCV infection promotes carcinogenesis through arousing chronic inflammation and the interaction between viral proteins and cell cycle regulatory factors [4]. Subsequently, hepatic stellate cells (HSCs) become activated. These activated HSCs not only interact with immune cells by secreting cytokines and chemokines, but also provoke excessive extracellular matrix (ECM) deposition and liver fibrosis, thus transforming the liver microenvironment into immunosuppressive [5,6]. Immune cells in the fibrotic liver, such as M2-type macrophages and regulatory T cells (Tregs), suppress anti-tumor immune responses, thereby facilitating tumor survival [7,8]. After entering the cirrhosis stage, the immune and non-immune cells, HSCs, and hepatocytes in the liver continue to interact to promote the occurrence of tumors [9]. The infiltration of macrophages in the liver, especially M2-type macrophages, and the secretion of related factors keep continually enhanced, thus promoting tumor invasion and metastasis [10,11]. Finally, the tumor microenvironment (TME) of HCC also undergoes metabolic reprogramming, which facilitates the continuous growth and survival of the tumor [12]. Overall, the dynamic interaction and evolution of various components within the TME drive the formation and progression of HCC. Instead of focusing on a static TME, this review depicted the evolution of the signaling pathways and molecular regulation in the dynamic TME. During this evolution, a "time window" may be utilized for precise treatment.

We systematically screened the existing literature by searching major databases, including PubMed, Web of Science, and Elsevier ScienceDirect. Studies dedicated to the TME of HCC over the past three years (2022–2025) were selected to guarantee the novelty of literature, mainly including original research studies, high-quality reviews, and key clinical trials published in peer-reviewed journals. Meanwhile, a small number of early foundational studies were also selected through methods such as manual screen-

ing of reference lists. In addition, studies irrelevant to the theme were excluded after reading their titles and abstracts, so as to ensure a high relevance of the literature to the present research theme.

2. Major Components in the HCC TME

The TME of HCC represents a highly intricate and dynamic ecosystem comprising tumor cells, various immune cells, stromal cells, ECM, and soluble factors, all of which interact intimately to influence the onset, progression, metastasis, and therapeutic responses of HCC. Notable immunosuppressive constituents include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), Tregs, and cancer-associated fibroblasts (CAFs). Conversely, cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells serve as the primary fighters against tumor growth. Other significant components include dendritic cells (DCs), tumor-associated endothelial cells (TECs), and tumor-associated neutrophils (TANs) (Fig. 1, Ref. [13,14]).

2.1 HCC Cells

HCC cells, the major player within the TME, actively modify their surrounding environment to enhance their survival, proliferation, invasion, and metastasis. HCC cells exhibit a substantial heterogeneity, as well as obvious intratumor and inter-tumor variations. A single HCC tumor displays a spatial heterogeneity. Its regions undergo distinct evolutions, resulting in multiple phenotypic subtypes that facilitate local adaptation of the tumor [15]. Guo *et al.* [16] delineated three subtypes of HCC tumor cells (metabolic, proliferative, and pro-metastatic), and the activation of the transforming growth factor-β (TGF-β)-Smad signaling pathway is critical for the epithelial-mesenchymal transition (EMT). HCC typically presents as multiple nodules carrying genomic, transcriptional, as well as immune landscape heterogeneity, which is associated with primary drug resistance [17]. This heterogeneity enables cancer cells to respond differentially to stimuli in the TME and select the clones most adaptive to the current microenvironment. For example, highly invasive cancer cells overexpress matrix metalloproteinases (MMPs), facilitating ECM degradation and paving a way for their own migration [13]. Residing within the TME of HCC, cancer stem cells (CSCs) possess self-renewal and pluripotent activity, closely correlating with the recurrence, metastasis, and drug resistance of HCC [18].

HCC cells engage in complex interactions with other cells within the TME, establishing an environment favorable for their growth. HCC cells can secrete various cytokines, growth factors and exosomes, to remodel the microenvironment. Tumor-derived alpha-fetoprotein (AFP) promotes macrophage polarization to an immunosuppressive phenotype and inhibits macrophage phagocytic function [19]. Besides, HCC cells secrete erythropoietin to activate the erythropoietin receptor signal in TAMs, promoting the construction of a tumor immunosuppressive microenvironment (TIME) [20]. HCC cells can transform normal HSCs into CAFs. Apart from secreting cytokines, tumor cells can also activate the protein kinase B (Akt) pathway in HSCs through exosomes, thereafter promoting the differentiation of HSCs into CAFs [21,22].

The exosomes released by HCC contain various bioactive molecules. Once internalized by other TME cells they deliver functional contents to target cells and alter their functions. For example, exosomes derived from cancer cells have been shown to interrupt the expression of neutrophil microRNA (miRNA) and activate the NF-κB pathway to induce neutrophil infiltration, finally resulting in T cell depletion [23]. Furthermore, exosomes can mediate the communication between cancer cells and distant cells. Previous research has shown that exosomes carrying specific miRNAs can activate the NF-κB pathway in lung fibroblasts, and help form pre-metastatic niches [24].

2.2 Accumulation of Immunosuppression-Related Cells

Immunosuppressive cells inhibit immune effector cells by upregulating inhibitory immune checkpoint molecules and producing immunosuppressive factors and chemokines, till the setup of the TIME. TAMs tend to grow into the M2 phenotype, exerting a variety of pro-tumorigenic effects [25]. During the close signaling between M2 macrophages and HCC cells, HCC cells secrete cytokines to recruit M2 macrophages, and then M2 macrophages TAMs promote tumor metastasis by facilitating angiogenesis, EMT, and vascular permeability [26]. Using a Transwell co-culture model, Zhang *et al.* [27] revealed bi-directional interactions between TAMs and HBV-associated HCC cells, which promoted M2 polarization as well as stemness maintenance of cancer cells. Wang *et al.* [28] demonstrated that M2 macrophages induce sorafenib resistance by secreting CXCL1 and CXCL2, with the downstream extracellular signal-regulated kinase (ERK) signaling playing a crucial role.

MDSCs suppress the immunity to promote tumor invasion, so a high MDSC infiltration is linked to a poor prognosis of HCC [29]. The main subtypes of MDSCs are polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs). PMN-MDSCs suppress T cell activity through the release of oxygenated lipids via ferroptosis [30]. They can also enhance their immunosuppressive function by upregulating the programmed death-ligand 1 (PD-L1) expression [31]. M-MDSCs exert immunosuppressive functions by inducing adenosine accumulation, which inhibits cluster of differentiation 8 $(CD8)^+$ T cell activity [32]. M-MDSCs can also highly express PD-L1 to induce $CD8^+$ T cell exhaustion, which is associated with liver transplant rejection [33]. Mutations in HCC induce the hyperactivity of β-catenin signals to recruit MDSCs [34]. MDSCs also affect the resistance to oxali-

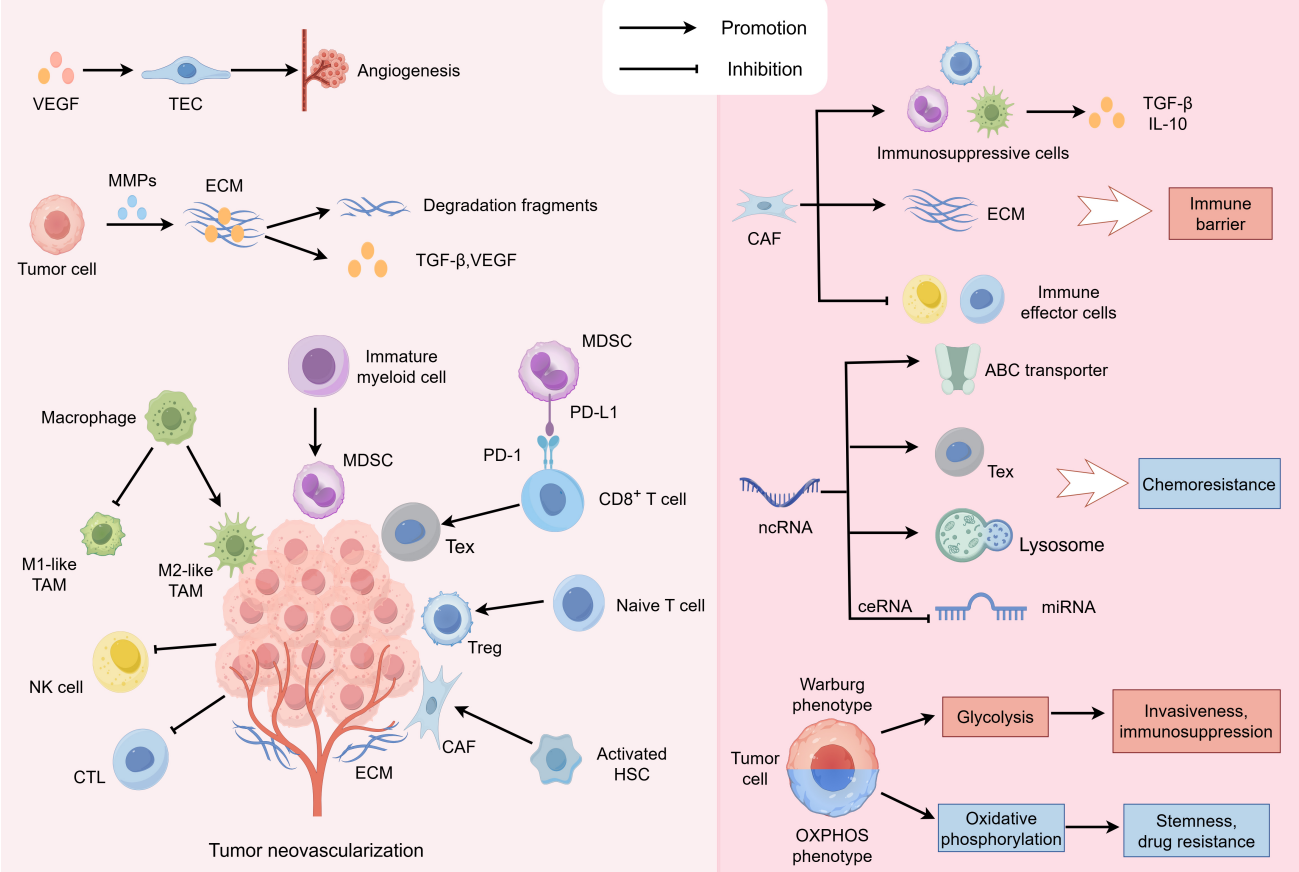

Fig. 1. Cellular interactions within the HCC TME. In the TME, tumor cells act as the core drivers, and immunosuppressive cells are enriched in their surroundings. Different HCC subtypes utilize unique glucose metabolism patterns (favoring either the Warburg effect or OXPHOS) to perform their distinct functions. Macrophages tend to differentiate into the immunosuppressive M2 phenotype, rather than the pro-inflammatory M1 phenotype; immature myeloid cells into MDSCs; naive T cells into Tregs; and activated HSCs into CAFs. And MDSCs can induce $CD8^+$ T cell exhaustion via the PD-L1/PD-1 pathway. Concurrently, the functionality of immune effector cells such as NK cells and CTLs is suppressed. Tumor cells are capable of secreting MMPs to degrade the ECM and liberate cytokines like TGF-β and VEGF, which are sequestered within the ECM [13]. VEGF can promote the proliferation of TECs and induce angiogenesis. CAFs are capable of recruiting immunosuppressive cells, generating ECM, and inhibiting the infiltration of immune effector cells, thereby forming an immune barrier [14]. Additionally, ncRNAs promote chemoresistance by inducing Texs and regulating ABC transporters, lysosomal function, and the ceRNA network. Abbreviations: MDSCs, myeloid-derived suppressor cells; HSCs, hepatic stellate cells; Tregs, regulatory T cells; NK cells, natural killer cells; CAFs, cancer-associated fibroblasts; CTLs, cytotoxic T lymphocytes; ECM, extracellular matrix; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; TECs, tumor-associated endothelial cells; Texs, exhausted T cells; CD8, cluster of differentiation 8; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; OXPHOS, oxidative phosphorylation; ncRNAs, non-coding RNAs; ABC, ATP-binding cassette; ceRNA, competing endogenous RNA; miRNAs, microRNAs; TAM, tumor-associated macrophage; TGF-β, transforming growth factor-β.

platin and sorafenib in HCC, and sorafenib cannot only recruit MDSCs but also enhance their function [35,36]. Liver transplantation is a vital therapeutic approach for HCC patients, but in a cohort of patients receiving liver transplantation (n = 331), M-MDSCs recruitment is linked to a high HCC recurrence rate [37]. Consequently, targeting MDSCs has garnered significant interest in the context of HCC treatment. Mei *et al.* [38] demonstrated that IL-37 can attenuate the immunosuppressive function of MDSCs in HCC through metabolic reprogramming.

Tregs, contributing to the immunosuppressive properties of the TME, present a major hurdle for immunotherapy to function in solid tumors. Tregs secrete a lot of immunosuppressive factors including TGF-β and IL-10, and express surface molecules such as programmed death 1 (PD-1) to promote HCC immune evasion [39]. In addition, Tregs secrete soluble fibrinogen-like protein 2, which inhibits maturation of DCs and promotes IL-35 secretion, thereby suppressing the activity of downstream $CD8^+$ T cells [40]. CCR8 Tregs are significantly enriched in HCC tissues, and the inhibition on CCR8 shifts the Tregs to lowly immuno-

suppressive and increases the abundance of antitumor cells [41]. Depletion of Tregs damages effector T cells (Teffs), so it is of clinical significance to distinguish between intratumoral and peripheral Tregs. Tumor-infiltrating Treg cells, specifically expressing CD177, enhance the immunosuppressive capacity to promote HCC development [42]. Anti-PD-1 treatment induces the infiltration of Tregs, whereas concomitant targeted inhibition on Tregs can boost the level of cytotoxic $CD8^+$ T cells to suppress tumor growth [43].

HCC cells recruit and activate CAFs to level up CAF infiltration, thus promoting tumor proliferation and metastasis linked to a poor prognosis [44]. Within HCC, many subgroups of CAFs display their own characteristics, and the heterogeneity of CAFs deserves special attention. For example, Periostin-positive CAFs, mainly located in the peripheral region of the tumor, can dominate ECM remodeling and induce macrophage M2 polarization, thus contributing significantly to the formation of an immune barrier [45]. Platelet-derived growth factor receptor α (PDGFRα)-positive CAFs, differentiated from hepatic progenitor cells (HPCs), can also recruit macrophages and induce M2 polarization [46]. Fibroblast activation protein-positive CAFs are enriched at HCC tumor boundaries and interact with TAMs to promote the formation of immune barriers [14]. The immune barrier prevents immune effector cells from entering the tumor, thereby creating immune rejection and reducing immunotherapeutic sensitivity. On the other hand, endosialin-positive CAFs inhibit $CD8^+$ T cell infiltration by reducing CXCL9/10 secretion [47]. By secreting laminin subunit alpha 4, $CD90^+$ CAFs can recruit and induce cellular senescence of $CD8^+$ T cells [48]. These subgroups may be targeted to design more treatment options for HCC.

2.3 Dysfunction of Immune Effector Cells

$CD8^+$ T cells and NK cells, two types of primary antitumor effector cells, can directly eliminate cancer cells. However, immune effector cells within the TME are often dysfunctional, limiting their efficacy in combating tumor growth. The accumulation of certain metabolites in HCC, such as glycerol-3-phosphate and bile acids, can diminish the cytotoxic capacity of CTLs [49,50]. Some cells in the TME can also inhibit the function of CTLs. For example, a subset of TECs secretes CXCL12 to suppress the activation of $CD8^+$ naive T cells [51].

In addition, chronic antigen exposure, such as persistent viral infections, activates the TOX and EOMES transcriptional programs, driving $CD8^+$ T cells into an "exhausted" state [52]. It is worth noting that under the upregulation of co-inhibitory receptors like PD-1 and immunosuppressive molecules like CD39, the immunosuppressive effect is amplified, indicating that Texs (exhausted T cells) also play an immunosuppressive role within the TME [52,53].

NK cells, integral to the innate immune system, act in anti-tumor immunity by recognizing and eliminating cancer cells without prior sensitization. In the TME of HCC, NK cells exhibit a low level, and their antitumor function is significantly inhibited. In addition, a study found that one type of bacteria in HCC can promote lipolysis into acetyl coenzyme A to inhibit NK cell ferroptosis and enhance the antitumor function of NK cells [54]. Although NK cells have antitumor effects, they can disrupt $CD8^+$ T cell differentiation by blocking retinoic acid receptor α-dependent differentiation programs, thereby discounting the efficacy of immune checkpoint inhibitors (ICIs) [55]. Therefore, excessive NK cells can make immunotherapy less effective. Additionally, tumor-associated regulatory NK cells can exert an immunosuppressive influence on MDSCs through the IL-6/STAT3 axis [56]. These findings highlight the multifaceted role of NK cells within the TME.

3. Key Signaling Pathways in the HCC TME

In the HCC TME, the abnormal activation of multiple key signaling pathways drives the hepatocarcinogenesis, progression, metastasis, and therapeutic resistance. These pathways form an intricate regulatory network underpinning cell proliferation, apoptosis, angiogenesis, and immune evasion. The main signaling pathways, functions, molecules and targeted drugs are summarized in Table 1 (Ref. [57–64]).

3.1 RTK Signaling Pathway

Receptor tyrosine kinases (RTKs), a category of surface receptors with transmembrane structures, exert a pivotal regulatory effect on HCC development. When bound by ligands such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), RTKs can activate downstream signaling cascades that collectively orchestrate cellular behaviors. The most common RTKs include vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), hepatocyte growth factor receptor (c-Met), and fibroblast growth factor receptor (FGFR). They are inhibited by tyrosine kinase inhibitors (TKIs) like lenvatinib [65].

The VEGFR signaling pathway mainly promotes tumor growth and spread by easing angiogenesis and increasing tumor blood supply. Abnormal vascular networks and angiogenesis in HCC are essential for growth, progression, invasion, and metastasis [66]. In addition, VEGFR, particularly VEGFR2, participates in TIME formation by facilitating Treg expansion, disrupting effector T cell and DC activities [67].

EGFR, integral to HCC proliferation and metastasis, also plays a role in establishing the TIME. Liver Kupffer cells depend on EGFR to produce IL-6, which stimulates compensatory proliferation and correlates with unfavorable survival outcomes in HCC patients [68]. Zhang *et al*. [69] demonstrated that EGFR participates in the formation of

Table 1. Key signaling pathways in HCC TME.

Signaling pathways	Functions	Key molecules	Targeted drug	Mechanism	Clinical phase	Refs.
RTK	Angiogenesis, immunosuppression, stem cell maintenance, drug resistance, anti-apoptosis	VEGF, VEGFR, EGF, EGFR, HGF, c-Met, FGF, FGFR	TKI (lenvatinib)	Inhibits VEGFR and FGFR pathways to suppress angiogenesis	III	[57]
ERK	Cell proliferation, invasion and metastasis, EMT, PD-L1 expression, immunosuppression, drug resistance	Ras, Raf, MEK, ERK	MEK inhibitor (refametinib)	Directly inhibits MEK to block ERK signaling and suppress abnormal proliferation	II	[58]
Wnt/β-catenin	Promote tumor growth and metastasis, EMT, immunosuppression	β-catenin, FZD, TCF/LEF, TBL1	TBL1 inhibitor (tegavivint)	Interferes with β-catenin-TBL1 binding to promote β-catenin degradation	I/II	[59]
TGF-β	Immunosuppression, EMT, angiogenesis, maintenance of stem cell stemness, fibrosis, drug resistance	TGF-β, TGF-βR, Smad	anti-ALK-1 monoclonal antibody (GT90001)	Blocks the TGF-β superfamily receptor ALK-1 to inhibit angiogenesis	Ib/II	[60]
PI3K/Akt/mTOR	Cell proliferation, metabolic regulation, immunosuppression, angiogenesis, drug resistance	PI3K, Akt, mTOR	mTOR inhibitor (everolimus)	Inhibits mTOR to block the cell cycle and suppress abnormal proliferation	II	[61]
Hedgehog	Cell proliferation, stem cell maintenance, drug resistance, immunosuppression, fibrosis	Hh, Smo, Gli	Smo inhibitor (vismodegib)	Inhibits Smo activation to cut off Hh pathway signaling	II	[62]
NF-κB	Stem cell maintenance, immunosuppression, EMT, drug resistance	IKK, NF-κB, TNF-α, IL-6	IKKα inhibitor (icaritin)	Binds to IKKα to block IKK complex formation, thereby inhibiting the NF-κB pathway and downregulating PD-L1 expression	III	[63]
HIF	Metabolic reprogramming, angiogenesis, stem cell maintenance, drug resistance, EMT, immunosuppression, promote metastasis	HIF-1α	HIF-1α mRNA inhibitor (RO7070179)	Directly inhibits HIF-1α expression, suppressing tumor proliferation and invasion	Ib	[64]

RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; FGF, fibroblast growth factor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; c-Met, hepatocyte growth factor receptor; FGFR, fibroblast growth factor receptor; TKI, tyrosine kinase inhibitor; PD-L1, programmed death-ligand 1; EMT, epithelial-mesenchymal transition; Ras, rat sarcoma; Raf, rapidly accelerated fibrosarcoma; FZD, Frizzled; TCF/LEF, T-cell factor/lymphoid enhancer factor; TBL1, transducin beta-like protein 1; TGF-β, transforming growth factor-β; TGF-βR, transforming growth factor-β receptor; ALK-1, activin receptor-like kinase 1; Akt, protein kinase B; Hh, Hedgehog; Smo, Smoothened; Gli, Glioma-associated oncogene homolog; IKK, IκB kinase; HIF, hypoxia-inducible factor; ERK, extracellular signal-regulated kinase; Wnt, wingless-type MMTV integration site family; MEK, MAPK kinase; PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin.

invasive pseudopodia of HCC cells, driven by increased stiffness of the ECM, and enhances the malignant traits of cancer cells. The activation of EGFR in HCC not only maintains the stemness and tumorigenicity of HCC cells, but also increases resistance to TKIs, such as lenvatinib and sorafenib, while targeted inhibition on EGFR can reverse this resistance [70–72]. Furthermore, this signaling pathway can interact with downstream signaling pathways to promote cancer progression. For instance, it stimulates the PI3K-Akt pathway to promote the Warburg effect and activate glycolysis to support the rapid proliferation of cancer cells, and also stimulate the downstream ERK1/2 pathway to encourage Treg differentiation and drug resistance [73–75].

As an oncogene, c-Met is overexpressed to promote the formation and proliferation of HCC [76]. HGF is the ligand for c-Met, and their binding activates downstream ERK1/2, rat sarcoma (Ras)/MAPK, and PI3K/Akt pathways to modulate HCC cell proliferation and migration [77]. In addition, the HGF-Met axis is a significant contributor to drug resistance and apoptosis resistance [78,79].

Fibroblast growth factor (FGF) and its high-affinity receptor FGFR can benefit tumor survival. On the one hand, it can induce the proliferation of hepatic endothelial cells and angiogenesis to support tumor metastasis [80]. On the other hand, it can also induce TAMs to cause tumor phenotypic changes, helping to form a TIME [81]. In a cohort study of 870 samples, FGFR4 is the most frequently expressed among HCC patients, implying it as a carcinogenic driver of HCC [82,83].

3.2 ERK Signaling Pathway

ERK is a subfamily of MAPKs that mediate various cellular responses, including inflammation, cell proliferation, cell differentiation, and apoptosis [84]. The classical MAPK pathway transmit signals through a highly conserved three-tiered cascade, in which the MAP kinase kinase kinase (MAP3K) phosphorylates the MAP kinase kinase (MAP2K) and then phosphorylates the MAPK to amplify signals for precise regulation [85]. Once activated, MAPKs target specific serine and threonine residues on downstream protein kinases or transcription factors, thus fulfilling a role in gene transcription [86]. Different MAPK subfamilies have their specific upstream kinases. Having been activated by rapidly accelerated fibrosarcoma (Raf) protein kinase, kinase MEK1 and MEK2 activate ERK1/2 [87]. Clinical studies have been conducted aiming to block the ERK pathway via MEK inhibitors [58].

The ERK signaling pathway modulates the immune response and the secretion of cytokines, including chemokines, TGF-β and colony-stimulating factors (CSFs), which recruit immunosuppressive cells and regulate their functions to remodel the TIME in HCC. In addition, the ERK pathway can upregulate the expression of PD-L1 and inhibit the immune response mediated by $CD8^+$ T cells [88].

In the context of HCC, the ERK pathway poses a profound effect on the myeloid TME. Activation of MEK-ERK1/2 drives cancer cells to secrete granulocyte-macrophage CSF, and monocyte-derived cells to develop with immunosuppressive and pro-inflammatory features [89]. Moreover, the glycolytic switch upregulates CD93 expression on monocytes through the ERK pathway, which enhances PD-L1 expression and also induces monocytes to produce the ECM component, thereby refraining $CD8^+$ T cells from migrating into the tumor [90]. High expression of AlkB homolog 5 (ALKBH5) in HCC can activate the ERK pathway through upregulating MAP3K8, which in turn increases the chemokine IL-8 expression to recruit PD-$L1^+$ macrophages [91]. ERK/NF-κB pathway, activated by S100 calcium-binding protein A9 in the TME, promotes the infiltration of PMN-MDSCs and upregulates PD-L1 expression [31]. Besides, the KRAS/MEK/ERK axis can elicit the overproduction of TGFβ1 which enhances the immunosuppressive function of Tregs [92].

The ERK pathway can transform tumor-associated cells immunosuppressive, and enhance their pro-tumorigenic effects. For example, the Raf/ERK pathway can be activated by lactate in-flow, which then induces macrophage M2 polarization and suppresses the immunity in HCC [93]. In addition, HBV can induce high IL8 production through triggering the MEK-ERK signaling, which not only enhances endothelial permeability to promote vascular invasion, but also switches Tregs polarization for easier immune escape [94].

The ERK pathway drives tumor growth, invasion, metastasis, and drug resistance. Deficient in p90 ribosomal S6 kinase 2, human HCC cells rely on the Ras/MAPK signaling pathway for proliferation, and this proliferation can be effectively curbed by MEK inhibitors [95]. The ERK pathway mediates TGF-β-induced secretion of extracellular vesicles which carry latent TGF-β cargo, thereby promoting tumor cells invasion [96]. M2-like TAMs produce chemokine CCL2 that can hijack the ERK pathway to increase zinc finger protein SNAIL expression, thus promoting EMT and tumor invasion [97]. According to Cai *et al.* [98], in cell lines SK-Hep1 and HepG2, a high expression of insulin-like growth factor 1 receptor boosts the proliferation and migration of sorafenib-treated cells by activating the Ras/Raf/ERK pathway.

3.3 Wnt/β-catenin Signaling Pathway

The Wnt/β-catenin signaling pathway, which is highly conserved, regulates various physiological and pathological processes, including cell proliferation, differentiation, and migration. In the Wnt/β-catenin signaling pathway, Wnt ligands interact with Frizzled (FZD) receptors to trigger a cascade of intracellular signaling events; ultimately, β-

catenin translocates into the cell nucleus, where it binds to transcription factors, T-cell factor/lymphoid enhancer factor (TCF/LEF) to regulate the expression of downstream genes [99]. The Wnt/β-catenin signaling pathway is often inactive in normal, fully developed livers, but becomes overactive to promote tumor growth and metastasis [100]. Many HCC patients show pathway-involved gene mutations. For example, a study involving 152 HCC patients revealed that 26.3% of patients carry Wnt/β-catenin mutations [101]. Approximately, one-third of HCC cases show gain-of-function mutations in CTNNB1 (β-catenin), with β-catenin activation correlating with the diminishment of T-cell infiltration [102]. Transducin beta-like protein 1 (TBL1) serves as a downstream target of this pathway, and tegavivint can target TBL1 to degrade β-catenin [103].

The Wnt/β-catenin signaling pathway is pivotal in the occurrence and progression of HCC. This pathway regulates the biological behaviors of HCC through interactions with stem cells, immune cells, tumor vessels, and non-cellular components [104]. A study showed that Wnt ligands from liver tumor cells can activate the Wnt/β-catenin signaling pathway in TAMs, promoting M2 polarization of TAMs and thereby enhancing immunosuppression [105]. Overexpression of β-catenin in HCC tumor cells can recruit MDSCs through the binding of platelet factor 4 to the CXCR3, thereby enhancing immune suppression [34]. In addition, once the Wnt/β-catenin pathway is activated within cancer cells, EMT is facilitated to confer cells with a migratory and metastatic capacity [106]. Inhibiting this pathway not only strengthens the efficacy of immune checkpoint therapy, but also the infiltration of immune effector cells [107,108].

3.4 TGF-β Signaling Pathway

The TGF-β signaling pathway exhibits a dual function in tumor biology, either inhibiting or promoting tumor growth depending on the profiles of cells and microenvironments [109]. During tumor development, the TGF-β signaling pathway frequently functions as a suppressor in the early stage, but as a promoter in later stages [110]. Within the HCC TME, the TGF-β pathway governs tumor progression through multiple mechanisms.

In response to chronic liver injury, TGF-β continuously activates HSCs to promote the massive deposition of collagen and other ECM components, thus increasing TME stiffness and forming a fibrotic microenvironment [111]. Fibrosis not only provides a protective barrier for tumor cells, but also activates such pathways as Yes-associated protein (YAP) through mechanical signals, consequently enhancing the stemness of CSCs in HCC [112]. Besides, fibrosis turns the TME immunosuppressive. TGF-β in the microenvironment interacts with downstream transcription factors Smad2/3 to inhibit immune effector cells, particularly $CD8^+$ T cells, resultantly undermining the antitumor immune response [113]. This immunosuppressive effect allows tumors to continually grow and spread, even under the host's immune surveillance. Moreover, the TGF-β signaling pathway can activate CAFs and secrete cytokines that promote tumor growth [114]. The chemokines CCL7 and CXCL16 secreted by CAFs can amplify the signaling of the TGF-β pathway in HCC cells, promoting their migration and invasion [115]. CAFs can also secrete TGF-β to form capillary-like structures, which can supply blood to HCC cells and tissues [116]. TGF-β, as a potent activator of ERK, can induce endothelial-mesenchymal transition to promote angiogenesis in the TME, and also impairs the endothelial barrier to facilitate tumor cells migration [117]. Additionally, the positive feedback loop of TGF-β signaling is linked with the stemness of CSCs and their resistance to therapeutic agents [118].

3.5 Other Signaling Pathways

The PI3K/Akt pathway is notably upregulated in patients with HCC [119]. The mTOR complex 1 (mTORC1), a vital downstream effector of the PI3K/Akt pathway, plays a key role in autophagy [120]. In HCC, autophagy occurs to promote tumor progression and drug resistance [121]. Within the TME, the activation of the PI3K/Akt pathway in TAMs promotes M2 polarization, allowing tumor cells to evade the immune system [122]. HBV-expressed hepatitis B surface antigen (HBsAg) and HBx can activate this pathway to induce cellular transformation, thus propeling the development of HBV-related HCC [123]. As an mTOR-targeted drug, everolimus remains under intensive investigation, despite its unsatisfactory results in previous trials [61].

The aberration of the Hedgehog (Hh) pathway is closely linked to oncogenesis. Hh ligands bind to inhibitory receptors Patched (Ptch) to disrupt the inhibitory effect to Smoothened (Smo), phosphorylating Glioma-associated oncogene homolog (Gli) transcription factors that move into the nucleus to initiate the transcription of target genes [124]. The Hh pathway can inhibit cell cycle arrest, promote HCC cell proliferation, and permit the self-renewal of liver CSCs, thus inducing an acquired drug resistance [125–127]. Previous research has shown that a key enzyme in cholesterol synthesis can activate the Hh signal to promote HCC regeneration and metastasis [128]. Hh signals can also stimulate various immune cells to foster an immunosuppressive vibe. Tumor cells secrete Hh ligands that drive PD-L1 expression in TAMs, which subsequently inhibits the $CD8^+$ T cell function [129].

Chronic inflammation is an important process involved in the development of HCC. The NF-κB signaling pathway is highly inflammation-related. Its activation requires the phosphorylation of the IκB by IκB kinase (IKK), and relieves its inhibition on NF-κB, allowing NF-κB to enter the nucleus [130]. The NF-κB pathway links inflammation with cancerigenesis. The TNF-α in the TME of HCC upregulates the expression of the transcription factor sal-

like protein 4 through the NF-κB pathway, maintaining the stemness and self-renewal of cancer cells [131]. This pathway can also promote the establishment of the TIME. It has shown that overexpressing NF-κB can upregulate PD-L1 to achieve immune evasion [132]. The NF-κB pathway can promote the EMT of HCC cells, giving cancer cells stronger capabilities to migrate and invade [133]. In addition, the activation of this pathway not only impairs the efficacy of immunotherapy and inhibits the sensitivity of HCC to chemotherapy, but also increases cancer cell resistance to radiotherapy [134–136]. Notably, blocking NF-κB signaling by inhibiting IKK has been shown to accelerate MYC-driven HCC [137]. This suggests that targeting this pathway for HCC treatment requires more in-depth research. Encouragingly, icaritin, a compound derived from traditional Chinese herbs, can inhibit NF-κB pathway with a promising therapeutic potential [138].

Owing to the outgrowth of tumor cells, oxygen within the tumor is overconsumed to create a hypoxic microenvironment. The hypoxia-inducible factor (HIF) pathway is dominant in the hypoxic response. Abnormal activation of the HIF pathway is involved in the occurrence, progression, metastasis, and treatment resistance of HCC. HIF regulates VEGF transcription and promotes the angiogenesis in HCC [139]. The activation of the HIF-1α pathway can increase the cancer stemness, as well as the acquisition of drug resistance [140]. Through driving metabolic reprogramming, HIF leaves tumor cells from aerobic oxidation to glycolysis under hypoxic conditions. HIF-1α can directly upregulate the expression of glycolysis-related enzymes. Hypoxia activates YAP, which binds to HIF-1α in the cell nucleus and promotes the transcription of glycolysis-associated genes [141]. Hypoxia induces functional changes in MDSCs through HIF-1α, promoting their differentiation into immunosuppressive TAMs [142]. Translational upregulation of HIF-1α in TAMs enhances glycolysis and significantly facilitates pro-tumor TAM polarization [143]. Moreover, HIF can regulate tumor invasion and metastasis. Hypoxia-induced tumor cell necrosis promotes the secretion of IL-1β from M2 macrophages, upregulates HIF-1α synthesis in HCC cells, enhances EMT in HCC cells, all coworking to promote tumor metastasis [144].

3.6 Crosstalk and Compensation of Signaling Pathways

Signaling pathways within the HCC TME do not function independently; rather, they form a complex regulatory network through intricate crosstalk, feedback loops, and compensatory mechanisms. As shown in (Fig. 2).

RTKs, upstream of the signaling cascade, can activate various downstream pathways, including the ERK and PI3K/Akt/mTOR pathways to promote tumor survival and proliferation [145,146]. Furthermore, RTKs can re-activate the ERK and Akt pathways, conferring HCC with a resistance to targeted therapies [147]. The PI3K/Akt pathway can then promote the translation of HIF-1α through mTOR [148]. And as a transcription factor, HIF-1α can indirectly modulate RTK signaling by uplifting ligand expression, thus forming a positive feedback loop [149]. Additionally, HIF-1α can regulate the transcriptional activity of NF-κB [150]. Simultaneously, NF-κB can directly upregulate HIF-1α expression, establishing crosstalk between inflammatory and hypoxic pathways [151]. For HIF-1α and TGF-β, their feed-forward loop plays a crucial role in the EMT of HCC [152]. The Wnt/β-catenin and Hh pathways are associated with cancer stemness [153]. The TGF-β/Smad3 signal can activate Gli2 in the non-canonical Hh pathway, promoting HCC invasion and increasing the risk of recurrence [154]. Gli2, in turn, can promote the production of Wnt ligands, which drives the formation of an immunosuppressive microenvironment [155]. Furthermore, Gli1 can trigger Wnt-β-catenin signaling, while Wnt can induce Hh signaling by raising Gli1 expression [156,157]. This crosstalk enhances cancer stemness as well as drug resistance.

Negative feedback is a common mechanism for maintaining biological homeostasis. The negative regulation of the pathway by growth factor-activated ERK involves a feedback loop, where activated ERK not only inhibits Raf activity via feedback phosphorylation but also promotes the expression of the downstream negative regulator, dual-specificity phosphatase (DUSP) [158,159]. Similarly, the activation of the PI3K/Akt/mTOR pathway not only increases the expression of its negative regulator, phosphatase and tensin homolog (PTEN), but also negatively regulates the pathway itself by inhibiting the expression of RTKs [160,161]. These negative feedback loops serve as a compensatory mechanism against single-target inhibitors, thus conferring drug resistance.Conversely, positive feedback amplifies pro-cancer signals, and the TGF-β/Smad pathway contains multiple positive feedback loops that promote HCC development [162]. For example, the activated TGF-β pathway upregulates the expression of the positive feedback regulator, TGF-beta receptor-associated binding protein 1 (TGFBRAP1), in CSCs, thereby amplifying the TGF-β signal and enhancing HCC drug resistance [118].

Targeting a single pathway with an inhibitor can easily trigger a compensatory effect from other pathways, suggesting that multi-target combination therapies may be more effective. For example, VEGF signaling can be selectively silenced to suppress tumor growth, but his suppression can also lead to hypoxia, resulting in HIF-1α accumulation, which drives HGF-Met signaling and enhances tumor invasiveness [163]. In addition, only a low ERK activity needs to be maintained during tumor progression, and simple inhibition on ERK often fails to exert a satisfactory antitumor effect, due to ERK's robust negative feedback mechanism [145]. Many ERK1/2 inhibitors are used in anti-tumor therapy, but the ERK5 compensation for ERK1/2 can lead to acquired resistance, which can be overcome with dual-target inhibitors [164].

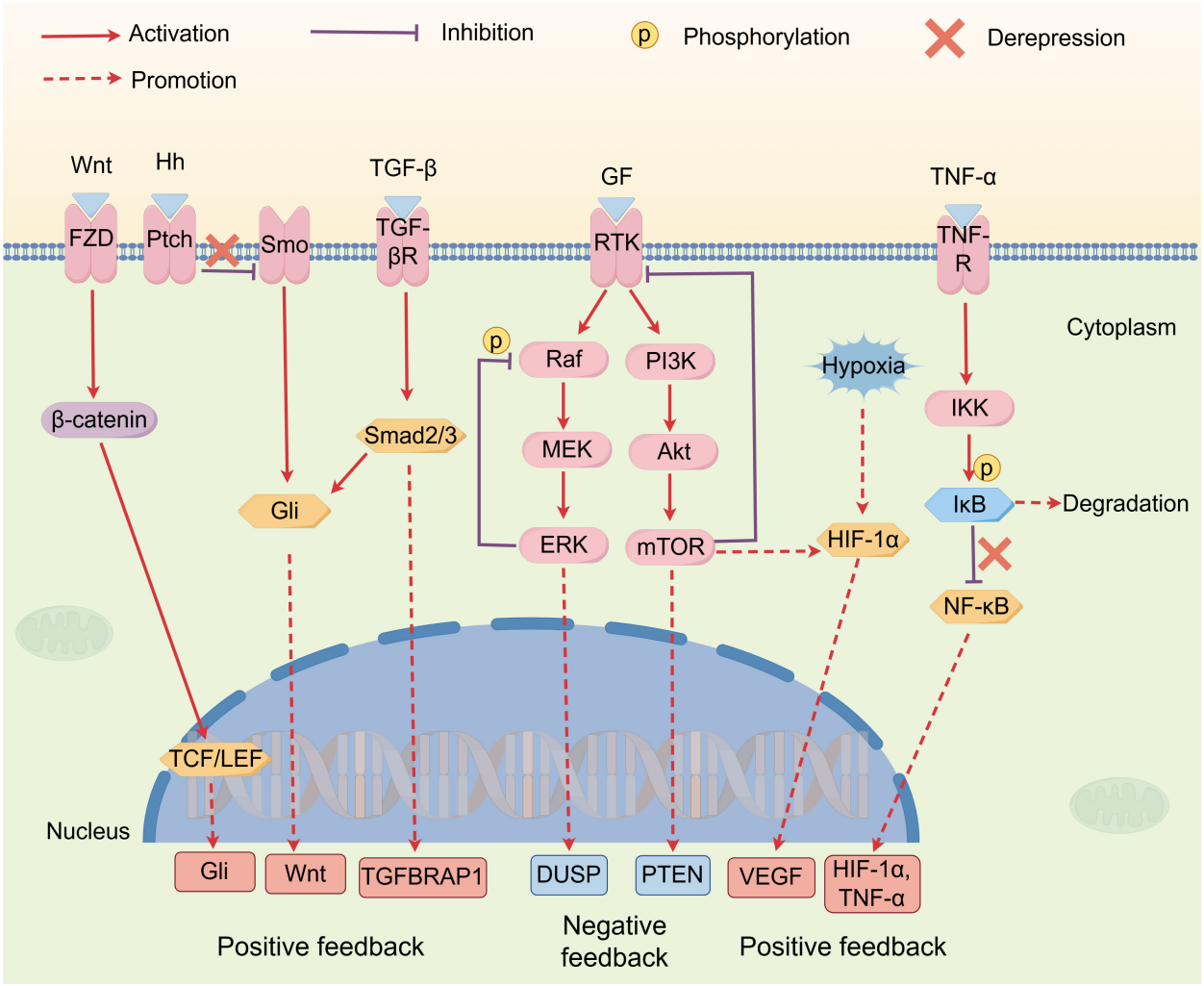

Fig. 2. Intricate network of signaling crosstalk. Crosstalk among various cellular signaling pathways forms a dynamic regulatory network. This network contains negative feedback mechanisms, such as the ERK and PI3K/Akt/mTOR pathways, which prevent pathway hyperactivation by inhibiting upstream signals and promoting the production of negative regulators. Simultaneously, the network also includes multiple positive feedback mechanisms that collectively drive tumor growth and drug resistance. For example, mTOR promotes the synthesis of HIF-1α, which in turn enhances VEGF expression, forming a positive feedback loop. The Wnt/β-catenin and Hh pathways also mutually promote each other. Additionally, the NF-κB and TGF-β pathways are involved in this complex positive feedback network. Abbreviations: GF, growth factor; RTK, receptor tyrosine kinases; Raf, rapidly accelerated fibrosarcoma; DUSP, dual-specificity phosphatase; Akt, protein kinase B; PTEN, phosphatase and tensin homolog; HIF, hypoxia-inducible factor; TNF-R, tumor necrosis factor receptor; IKK, IκB kinase; TGF-β, transforming growth factor-β; TGFBRAP1, TGF-beta receptor-associated binding protein 1; Ptch, Patched; Smo, Smoothened; Gli, glioma-associated oncogene homolog; FZD, Frizzled; TCF/LEF, T-cell factor/lymphoid enhancer factor; Smad2/3, Sma and Mad-related proteins.

4. Molecular Regulation in the HCC TME

4.1 Immune Checkpoint Molecules

PD-1, an immune checkpoint molecule predominantly expressed on T cells, interacts with PD-L1, which is mainly located on tumor cells, macrophages, and DCs. This interaction facilitates tumor cell proliferation and dissemination by suppressing immune responses [165]. The expression of PD-L1 is intricately linked to immune evasion, and its interaction with PD-1 induces T cell dysfunction and exhaustion [166]. A study on HCC demonstrated that a high PD-L1 expression correlates with aggressive tumor characteristics and poor clinical outcomes [167]. Additionally, PD-L1 overexpression may facilitate tumor progression via evoking the Akt/β-catenin signaling pathway [168]. In the TME, PD-L1 expression is not confined in tumor cells, but also infiltrating immune cells. For instance, a study by He *et al.* [169] demonstrated that PD-L1 is expressed on tumor-infiltrating neutrophils, further quelling adaptive immune responses and facilitating tumor immune evasion. Moreover, PD-L1 expression is regulated by var-

ious factors, such as inflammatory cytokines and metabolites in the TME. For example, tumor-derived lactate can regulate PD-L1 expression on neutrophils through related pathways, thereby inhibiting the response of anti-tumor immunity [170].

Beyond PD-1/PD-L1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a classic immune checkpoint molecule, significantly contributes to the progression of HCC. High CTLA-4 expression contributes to the construction of the TIME, which involves various mechanisms that impair the ability of the immune system for tumor surveillance and clearance, including the secretion of inhibitory cytokines and metabolites [171]. CTLA-4 maintains immune tolerance primarily by inhibiting T cell activation, thus fostering tumor proliferation and immune evasion [172].

T cell immunoglobulin and mucin-domain containing-3 (TIM-3), a newly found immune checkpoint molecule, is broadly expressed on various immune cells, and commit multiple roles in the TME. Tan *et al*. [173] demonstrated that TIM-3 promotes HCC progression by impairing the function of NK cells: specifically, TIM-3 is upregulated in tumor-infiltrating NK cells and inhibits their cytokine-secreting and cytotoxic abilities. Thus, blocking TIM-3 can restore NK cell function and suppress HCC growth. Additionally, TIM-3 inhibition can enhance the ability of DCs to regulate innate and adaptive immunity and promote the M2-to-M1 polarization of macrophages, thereby countering tumor progression [174].

Another immune checkpoint molecule is lymphocyte-activation gene 3 (LAG-3), and its expression is also closely linked to the transformation into TIME. A study found that the co-expression of LAG-3 and PD-1 may further suppress T cell function, suggesting that the blockade of both LAG-3 and PD-1 may open a new therapeutic avenue [175].

4.2 Soluble Factors and Exosomes

Cytokines in the HCC TME not only regulate immune responses, but also tumor growth, invasion, and metastasis through multiple mechanisms. TAMs secrete cytokines, such as TGF-β1, to promote EMT, thereby enhancing the stem-like properties and invasiveness of tumor cells [176]. Moreover, cytokines are indispensable for the formation of TIME. Immunosuppressing cells in the TME, such as MDSCs, secrete cytokines like IL-10 and TGF-β to inhibit the activation of Teffs, thereby facilitating tumor immune evasion [177].

Furthermore, chemokines, a specialized subset of cytokines, precisely guide immune cells to migrate to the TME during tumor progression. Specifically, they interact with their receptors to regulate the accumulation of immune cells, thereby transforming the TME, so the expression and activity of chemokines and their receptors are inevitably closely related to cancer prognosis [178,179]. For example, CXCL12 can support tumor growth and metastasis by abnormalizing the biological properties of endothelial cells [51]. Liu *et al*. [180] found that CCL15 promotes immune evasion in HCC by recruiting $CCR1^+$ monocytes. Chemokines, such as CXCL5, not only function in tumor progression, but also may serve as diagnostic and prognostic biomarkers [181].

Exosomes, as a mediator on intercellular communication, also exert multiple biological functions in the HCC TME. First, exosomes derived from HCC cells can deliver biomolecules to disrupt the function of immune cells, promoting the formation of TIME. For example, non-coding RNAs (ncRNAs) in exosomes can promote the expansion of Tregs to interfere with the immune system and thereby promote tumor proliferation and metastasis [182]. Second, exosomes are integral to the processes of metastasis and invasion in HCC. For example, exosomal miR-92a-3p derived from cancer cells with a high metastatic potential enhances the EMT and metastasis of low-metastatic cancer cells by modulating the PTEN/Akt pathway [183]. Additionally, exosomes released by HCC cells can disturb the action of drugs by delivering specific RNA molecules and proteins, leading to drug resistance [184]. Finally, exosomes have shown potential values in diagnosing and treating HCC: either as biomarkers for early diagnosis and prognosis, or carriers for targeted drug delivery [185,186].

The mechanisms by which ncRNAs act in the TME have slipped into the research hotspot in recent years. ncRNAs influence tumor immune evasion and immune responses by regulating immune cell infiltration and activation. It can shape the TIME by regulating the polarization of TAMs, thereby influencing HCC progression [187]. Besides, ncRNAs are implicated in the proliferation, invasion, and metastasis of tumor cells. Xue *et al*. [188] found that certain long non-coding RNAs (lncRNAs) tune the proliferation and migration of HCC cells through interactions with proteins. Additionally, ncRNAs regulate the expression of pivotal genes through a competing endogenous RNA (ceRNA) mechanism during the occurrence and development of HCC [189]. Multiple ncRNAs can upregulate ATP-binding cassette (ABC) transporters, which promotes the efflux of chemotherapy drugs [190]. By promoting chemotherapy drug efflux and immune evasion, ncRNAs can mediate cancer cell drug resistance, which positions them as promising biomarkers and therapeutic targets [191]. For example, cancer cell-derived lncRNA HDAC2-AS2 promotes $CD8^+$ T cell exhaustion and inhibits anti-tumor immunity [192]. LINC00680 can activate Akt3 to decrease the chemosensitivity of HCC to 5-fluorouracil [193]. LINC-ROR enhances resistance to adriamycin by activating the Wnt/β-catenin pathway [194]. Both lncRNAs and circular RNAs (circRNAs) can act as competing sponges via the ceRNA mechanism. By binding to and inhibiting the function of tumor-suppressive miRNAs, they upregulate downstream pro-cancer signaling pathways or suppress apoptosis signals, ultimately leading

to drug resistance in HCC cells [136,195]. The lncRNA KCNQ1OT1 can act as a sponge for tumor-suppressive miRNAs, thereby activating pro-cancer signals and leading to chemoresistance [196]. Furthermore, ncRNAs are also capable of regulating lysosomal function, and through drug lysosomotropism, they diminish the therapeutic effect of chemotherapy [197].

Although they have the potential to serve as biomarkers, their clinical translation still faces significant challenges. While chemokines can predict therapeutic responses, their clinical translation is hampered by a lack of large-scale, prospective studies [198]. Similarly, although exosomes show favorable predictive sensitivity and specificity, their extraction and isolation are technically demanding, and their functional mechanisms require in-depth investigations [199].

4.3 Metabolic Reprogramming

Metabolic reprogramming, a significant hallmark of HCC, is engaged in the proliferation, survival and immune evasion of tumor cells. In HCC, dysregulation of glucose, fatty acid, and amino acid metabolism represents a key component in metabolic reprogramming, and significantly distorts the functions of TAMs and other immune cells [200]. Reprogramming of glucose metabolism is one of the most significant metabolic changes in HCC, with HCC cells tending to acquire energy via glycolysis rather than oxidative phosphorylation (OXPHOS)—a phenomenon known as the "Warburg effect" [201]. Under the Warburg effect, HCC cells preferentially produce energy through glycolysis, even under aerobic conditions, manifesting increases in glucose uptake and lactate production. Cancer cells exhibit metabolic plasticity, where OXPHOS is not abolished but co-regulates energy provision with glycolysis [202]. Some HCC subtype cells with reactivated OXPHOS tend to generate energy through the oxidative phosphorylation pathway, resulting in oxygen overconsumption [203]. And OXPHOS is also associated with cancer stemness maintenance and drug resistance, driving the development of OXPHOS inhibitors [204]. The shift in metabolic pathways not only satisfies the demands of cancer cells for rapid proliferation, but also provides a microenvironment conducive for tumor advancement [205].

Fatty acid metabolism is also reprogrammed in HCC. Obesity and metabolic dysfunction-associated steatohepatitis (MASH) are recognized as risk factors for HCC; under these conditions, fatty acid metabolic reprogramming provides tumor cells with abundant exogenous fatty acids, thereby promoting tumor progression [206]. This reprogramming not only drives the growth of tumor cells, but also promotes them to release metabolites to interact with other non-cancerous cells, leading to the acidification of microenvironmental and suppression on immune cell activity [207].

Reprogramming of amino acid metabolism, particularly that of glutamine, also plays a vital role in the occurrence and development of HCC. Glutamine metabolism provides carbon and nitrogen sources for HCC cells, which are used for the synthesis of glutathione and nucleotides, promoting cell proliferation [208]. In addition, glutamine metabolism is also associated with the activation of the mTOR signaling pathway, which hinders immunotherapy [209]. In summary, metabolic reprogramming in HCC reshapes the TME through multiple pathways to promote tumor progression and immune evasion.

4.4 Gut Microbiota-Derived Metabolites in HCC

The metabolites derived from the gut microbiota exert a dual effect on HCC through the gut-liver axis. Short-chain fatty acids from a balanced microbiota can suppress HCC. For example, butyrate can stimulate the production of chemokines, thereby favoring the infiltration of NK cells [210]. Isobutyrate suppresses tumor growth by augmenting $CD8^+$ T cells and muting the JAK/STAT3 pathway [211]. Conversely, dysbiotic gut microbiota can accelerate the intrahepatic metastasis of HCC [212]. A reduction in vitamin B6 synthesis by dysbiotic microbiota can disrupt the amino acid metabolism, and impair the function of immune cells in HCC [213,214]. Moreover, the dysregulation of secondary bile acids (BAs) metabolism is linked to carcinogenesis. Owing to the scarcity of gut bacteria rich in bile salt hydrolase, obesity induces increases in carcinogenic deoxycholic acids and reductions in protective secondary BAs, jointly promote tumor growth [215,216]. Additionally, due to the impairment of intestinal barrier in pathological conditions, excessive lipopolysaccharide (LPS) enters the liver through intestinal leakage, binds to TLR4 on hepatocytes, and enhances the invasive capacity of HCC [217].

5. Microenvironmental Changes Prior to Tumorigenesis

Before tumorigenesis, the hepatic microenvironment is remodeled profoundly and dynamically, creating a niche favoring tumor initiation and progression (Fig. 3, Ref. [124, 218–222]).

5.1 Hepatitis

As the initial stage of HCC, hepatitis is a vital contributor to the development of HCC. Its inflammatory microenvironment provides the basis for subsequent lesions to build up. Many signaling pathway start to show abnormalities during this stage. Persistent inflammation in the liver can cause hepatic injury and fibrosis, thus elevating the risk of cancer. During the chronic inflammatory phase, pro-inflammatory cytokines like TNF-α can activate the JNK signaling pathway, thereby transforming Smad3 phosphoisoform signals from tumor suppressive to oncogenic, as well as promoting the development of HCC [223]. Viral infection and metabolic disorders are the main causes of hepatitis.

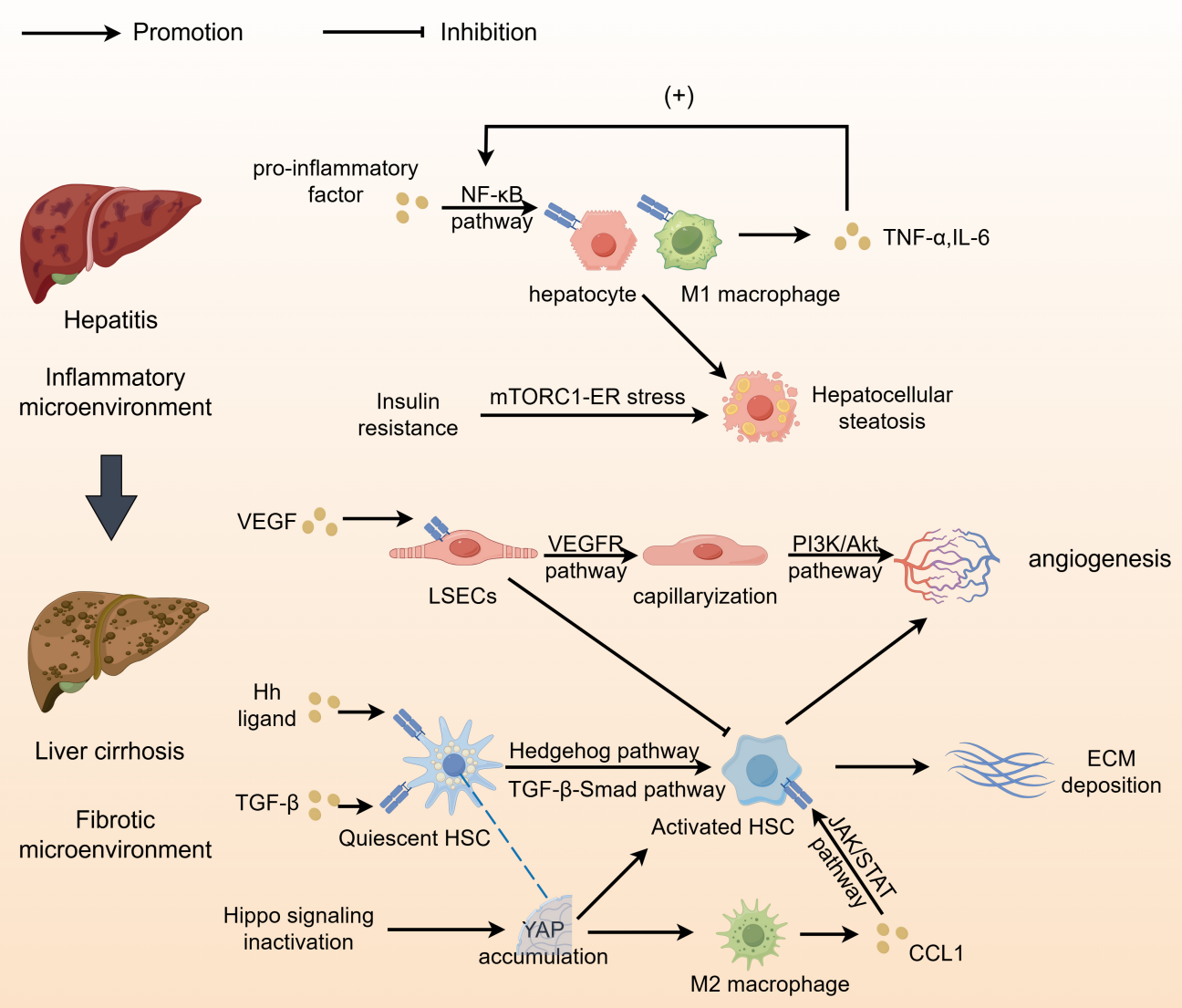

Fig. 3. Microenvironmental changes during different stages of chronic liver diseases. During the phase of hepatitis, an inflammatory microenvironment predominates. Pro-inflammatory factors trigger the NF-κB pathway in hepatocytes and M1 macrophages, and promotes the secretion of pro-inflammatory factors like TNF-α and IL-6, which in turn forms a positive feedback loop exacerbating hepatic steatosis [218]. Insulin resistance and the mTORC1-ER stress pathway jointly contribute to the formation of fatty liver. In the cirrhotic phase, a fibrotic microenvironment predominates, mainly composed of activated HSCs, favoring ECM deposition and angiogenesis. The Hh pathway, TGF-β-SMAD pathway, and the inactivation of Hippo signaling pathway leading to YAP accumulation in the nucleus can all activate HSCs [124,219,220]. YAP accumulation can also recruit macrophages and polarize them towards M2 to secrete CCL1, thus activating the JAK/STAT pathway in HSCs and accelerating the progression of liver fibrosis [221]. Additionally, the VEGFR2-dependent PI3K/Akt pathway causes capillarization of LSECs to promote angiogenesis [222]. Abbreviations: mTORC1, mTOR complex 1; ER, endoplasmic reticulum; HSCs, hepatic stellate cells; YAP, Yes-associated protein; ECM, extracellular matrix; Hh, Hedgehog; TGF-β, transforming growth factor-β; Akt, protein kinase B; VEGFR2, vascular endothelial growth factor receptor 2; LSECs, liver sinusoidal endothelial cells.

Viral infection stands as the principal cause of hepatitis, especially HBV, and chronic hepatitis B constitutes a high-risk factor for HCC. In the context of HBV infection, the HBx continuously activates the NF-κB signaling pathway in hepatocytes, driving the massive secretion of inflammatory cytokine IL-6 and creating a pro-inflammatory microenvironment [224]. In addition, hepatitis B core antigen elevates the expression of TLR2 in M2 macrophages, activates downstream NF-κB signaling, ultimately damaging the M2 phenotype and heightening its proinflammatory capacity [225]. However, HBsAg suppresses the innate antiviral immune system through inhibiting the NF-κB signaling pathway, helping the virus escape the immune response and maintaining the state of infection [226,227].

Moreover, the dysbiosis of the gut microbiota is intimately connected with chronic liver disease. LPS from gut Gram-negative bacteria enter the bloodstream and are transported to the liver, where LPS binds to TLR4 on Kupffer cells and other cells, activating the LPS/TLR4 signaling pathway, as well as the MAPK and NF-κB inflammatory pathways [228,229]. In addition, bacteria can also produce ethanol, which further produces acetaldehyde, an intermediate product, in the liver, thereby exacerbating oxidative damage to the liver [228]. Various pro-inflammatory factors of both intrahepatic and extrahepatic origin, such as LPS from the intestine, can activate NF-κB-dependent pathways in hepatocytes and macrophages to upregulate TNF-α expression, and TNF-α interacts with tumor necrosis factor receptor 1 (TNF-R1) to activate the classical NF-κB pathway, thereby establishing a positive feedback cycle that exacerbates hepatic steatosis [218].

The incidence of MASLD/MASH has kept rising steadily in recent years. In MASLD/MASH, Hh signaling is consistently involved, as liver injury increases the secretion of Hh ligands to activate the Hh pathway, thus facilitating the deterioration from MASLD to HCC [124]. The Hh pathway not only promotes MASH progression, but also regulates HSC-mediated angiogenesis in liver fibrosis and the malignant conversion of the TME in HCC [124]. Hu *et al*. [230] found that ductal reaction originating from HPCs can activate the Hh pathway and promote liver fibrosis. Highly sensitive to energy metabolism, the mTORC1 signaling promotes lipid synthesis, increases lipid storage, impairs insulin signaling, and triggers inflammation in MASLD, thereby resulting in insulin resistance [231]. High-level fructose can activate the mTOR-autophagy-endoplasmic reticulum (ER) stress signaling pathway to inhibit hepatic autophagy, increase ER stress, enhance fatty acid synthesis, form fatty liver; then with activation of inflammatory pathways, fibrosis is induced, thus accelerating the advancement of chronic liver disease [232]. The AMP-activated protein kinase (AMPK) pathway, closely implicated in lipid metabolism, inhibits lipid formation and promots fatty acid oxidation [233]. Some natural compounds, such as acacetin and Buddleoside, have been found to target and inhibit mTORC1, enhance the AMPK signaling pathway, activate autophagy mediated by the transcription factor EB, reduce fat accumulation, and ultimately alleviate MASLD [234,235]. Smad is a downstream signaling molecule of the TGF-β pathway. Yang *et al*. [236] found that in the development of MASLD, Smad4 activates the MAPK signaling pathway to increase CXCL1 secretion, induce hepatocyte lipogenesis, and tilt macrophage polarization to the proinflammatory M1 type, whereas the activation of Smad4 is independent of TGF-β.

5.2 Cirrhosis

Cirrhosis, a progressive disease, is characterized by liver fibrosis, nodule formation, and functional impairment, and its progression parallels with the changes in the liver microenvironment. This microenvironment serves as a physical support for hepatocytes, and also a complex ecosystem undergoing cell-cell interactions, ECM remodeling, and crosstalk among diverse signaling molecules.

Liver fibrosis, either as the consequence of persistent inflammation and or the preliminary stage of cirrhosis, is mainly related to the activation of HSCs. Liver fibrosis is mainly reflected as the changes in the ECM. Activated quiescent HSCs differentiate into myofibroblastic HSCs to promote the deposition of ECM, thus increasing the stiffness of the ECM, which in turn activates of HSCs and worsens liver fibrosis [237]. THe TGF-β signaling is responsible for activation of HSCs and progression of liver fibrosis [219]. Blocking the TGF-β pathway can prevent HSC activation [238]. Zhang *et al*. [239] found that growth differentiation factor 10 specifically inhibits TGF-β-Smad2/3 signaling in HSCs, thereby suppressing the activity of HSCs. In addition, non-Smad-dependent pathways, such as MAPK pathway, are also involved in HSC activation and ECM production [240]. For example, the activation of the PI3K/Akt pathway in hepatocytes increases exosome release and then stimulates the Smad3 pathway in HSCs, thereby activating HSCs and promoting fibrosis [241]. YAP is a transcription cofactor dedicated to fibrosis [242]. During a normal liver homeostasis, the Hippo signaling pathway is active to leave YAP phosphorylated and inactivated, thereby limiting the enlargement of the liver. But in abnormal liver tissue repair, the Hippo signaling is masked, thus leading to YAP accumulation, HSC activation and fibrosis, as well as the shift of macrophages towards the M2 phenotype [220].

Macrophages also takes on a critical profile in the microenvironment of cirrhosis. They secrete various cytokines and chemokines that act on HSC activation and inflammatory responses. Macrophages can promote or inhibit hepatic fibrosis during cirrhosis. Macrophage-secreted CCL1 can target and activate the CCR8 on HSCs, thereby igniting the JAK/STAT signaling pathway and accelerating the progression of liver fibrosis [221]. Silencing the JAK/STAT pathway in HSCs can impede EMT to alleviate liver fibrosis [243,244]. However, the monocytes can also pool to differentiate into reparative macrophages, which primarily express MMPs and induce the regression of fibrosis [245]. Given their high heterogeneity and plasticity, macrophages reprogramming therapy may be feasible for liver diseases. In addition, in the decompensated stage of cirrhosis, the abundance of follicular helper T cells decreases and the intensity of IL-2 signaling increases, collaboratively triggering cirrhosis-related immune dysfunction [246].

Moreover, the capillarization of liver sinusoidal endothelial cells (LSECs) is observed over the progression of cirrhosis. Healthy LSECs, characterized by transcellular pores and the absence of basement membranes, inter-

act with surrounding cells through angiocrine signaling to maintain liver homeostasis [247]. In the context of liver injury, LSECs lose their membrane fenestrae and function to regulate blood flow, manifesting abnormal liver hemodynamics and hypoxia; meanwhile, they lose their ability to maintain HSCs quiescent, further promoting fibrosis [247]. VEGFR and other angiogenesis-related signaling pathways undertakes a central role in the phenotypic changes of LSECs. The VEGFR2-dependent PI3K/Akt pathway in LSECs promotes angiogenesis, which in turn induces liver fibrosis [222].

5.3 Dynamic Therapeutic Windows

The progression from hepatitis to HCC is a complex process characterized by dynamic changes in cellular signaling pathways. Each stage of this disease is dominated by distinct signaling characteristics. Therefore, a targeted approach to inhibit these stage-specific pathways may offer a promising strategy to slow down disease progression. Further clinical studies are summarized in Table 2.

The TLR and NF-κB signaling pathways play critical roles in hepatitis occurrence and innate immunity [248]. TLR is a key signal upstream NF-κB. Viral infections suppress TLR7 expression to shift hepatitis to cirrhosis and HCC [249,250]. TLR7 agonists, such as nucleoside or nucleotide analogue (a class of antiviral drugs), can arouse the innate immunity to combat viral hepatitis [251]. The TGF-β pathway is tightly involved in liver fibrosis and cirrhosis, but a direct inhibition on TGF-β is difficult to be achieved, due to its dual effects. Correspondingly, researchers have chosen to inhibit key downstream targets, such as lysyl oxidase-like 2 (LOXL2), but the results remain far from ideal [252]. For advanced HCC, the combination of anti-angiogenic therapy with immunotherapy produces a powerful synergistic effect. AFP response and anti-PD-1 autoantibodies can serve as potential prognostic biomarkers [253,254].

6. Clinical Therapy

Despite some breakthroughs in the treatment of hepatitis and liver cirrhosis, the field faces major challenges due to the complex interplay of multiple signaling pathways and the irreversibility of late-stage fibrosis. As a result, many patients still progress from cirrhosis to HCC, which has made HCC a central focus for drug development in liver diseases.

As suggested by the ESMO guidelines, a range of treatments, such as liver resection, thermal tumour ablation, liver transplantation, radiotherapy and transarterial therapies, can be adopted to fight early HCC [255]. But HCC is usually not suitable for surgery due to its high aggressiveness, as it has usually already spread or invaded important blood vessels at diagnosis. Consequently, targeted therapy and immunotherapy may bring with encouraging results in HCC treatment [256]. Several targeted drugs and immunotherapeutic agents, which have been evaluated in clinical trials in recent years, are listed in Table 3.

6.1 Targeted Therapy

Angiogenesis is a prerequisite for the rapid growth and metastasis of HCC. Targeting receptors such as VEGFR can inhibit tumor angiogenesis. As multi-targeted TKIs, sorafenib and lenvatinib have been approved as the first line for the treatment of advanced HCC, but adverse reactions and drug resistance limit their application [65,257]. As the cornerstone in the second line, regorafenib and cabozantinib are multi-kinase inhibitors that can prolong OS in patients with advanced HCC who show progression after sorafenib treatment [258–260]. Ramucirumab, a monoclonal antibody that specifically targets VEGFR-2, is specifically selected to treat HCC patients with elevated AFP [261]. Apart from above drugs recommended in the guidelines, apatinib and donafenib have also received approval in China for HCC [262–264]. Other new drugs, such as anlotinib, have shown therapeutic potential and controllable safety in both first-line and second-line treatments [265]. Tivozanib and fruquintinib have been approved for other cancers, but their efficacy for HCC should be further explored [266].

Galunisertib, as a TGF-β receptor I (TGF-βRI) inhibitor targeting tumor stroma, fails to achieve an optimal efficacy, and other targeted drugs are still under clinical investigation. For example, GT90001 inhibits activin receptor-like kinase 1 (ALK-1)/TGF-β signaling and tumor angiogenesis, and its combination therapy has been explored in clinical trials [60]. Drugs are also available to target the Hh pathway, such as vismodegib, but their efficacy for HCC is still being evaluated in the research and remains unclear [124].

Refametinib, an MEK inhibitor, has been found to exhibit synergistic antitumor effects for RAS-mutated HCC when used in combination with sorafenib [58]. The mTOR inhibitor sapanisertib is currently assessed in the clinical trial. Moreover, early clinical trials have employed mRNA antagonists to inhibit HIF1α, a core element in the hypoxic response pathway [64].

6.2 Immunotherapy Combined With Targeted Therapy

The immunosuppression in the HCC TME is the primary obstacle that the immunotherapy aims to resolve. Such suppression can be relaxed to reactivate the host's intrinsic anti-tumor immune response. Therefore, the immunotherapy is often combined with targeted therapy.

ICIs, the cornerstone of HCC immunotherapy, can restore T lymphocyte activity by blocking immune checkpoint molecules to strengthen cancer cell recognition and killing. ICIs are often used in combination with anti-angiogenic agents. The combination of atezolizumab (a PD-L1 inhibitor) and bevacizumab (an anti-VEGF monoclonal antibody) serves as the first-line defense against advanced HCC. Atezolizumab blocks the binding of PD-L1

Table 2. Clinical interventions for HCC across the hepatitis-fibrosis-HCC continuum.

Disease stage	Primary signaling pathways	Biomarkers	Drugs	Target Disease	Mechanism	Clinical Trial
Hepatitis	NF-κB, TLR, GLP-1R, GCGR, FGFR	IL-1	Canakinumab	Alcoholic hepatitis	Inhibition of inflammation by suppressing the key mediator IL-1β	NCT03775109 (Completed)
		TLR7 mRNA	RO7020531	Chronic hepatitis B	Enhancement of adaptive immunity via TLR7 activation	NCT02956850 (Completed)
		HFF	Cotadutide	MASH	Improvement of hepatic steatosis through GLP-1R/GCGR co-agonism	NCT05364931 (Completed)
		Adiponectin concentration, PRO-C3	BMS-986036	MASH	Regulation of lipid and glucose metabolism as an FGF21 analog	NCT03486912 (Completed)
Liver fibrosis/ liver cirrhosis	TGF-β	p-Smad3	Pirfenidone	Liver fibrosis	Suppresses the phosphorylation of signaling proteins in the TGF-β1 pathway	NCT05542615 (Unknown status)
		Smad7, TGFβRI	Hydronidone	Liver fibrosis associated with chronic hepatitis B	Promotion of TGFβRI degradation via enhanced Smad7 expression	NCT05115942 (Completed)
		LOXL2	Simtuzumab	Compensated cirrhosis	An anti-LOXL2 monoclonal antibody that blocks a key step in liver fibrosis	NCT01672879 (Terminated)
HCC	RTKs, PD-1/PD-L1, CTLA-4	AFP, Anti-PD-1 autoantibody	Bevacizumab+atezolizumab	Locally advanced or metastatic HCC	Simultaneous inhibition of VEGF and PD-L1 to block angiogenesis and immune evasion	NCT03434379 (Completed)
		FGFR4 and Treg infiltration	Lenvatinib+pembrolizumab	Advanced HCC	Targets VEGFR, FGFR, and PD-1 to counter angiogenesis and immune suppression	NCT03713593 (Completed)
		NLR	Durvalumab+tremelimumab	Advanced HCC	Synergistic activation of anti-tumor immunity via PD-L1 and CTLA-4 inhibition	NCT03298451 (Completed)

GLP-1R, glucagon-like peptide-1 receptor; GCGR, glucagon receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HFF, hepatic fat fraction; MASH, metabolic dysfunction-associated steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; TGF-β, transforming growth factor-β; TGFβRI, TGF-β receptor I; LOXL2, lysyl oxidase-like 2; HCC, hepatocellular carcinoma; RTKs, receptor tyrosine kinases; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; AFP, alpha-fetoprotein; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Agents from recent clinical trials on targeted therapy, immunotherapy, and immunotherapy combined with targeted therapy for HCC.

Treatment		Clinical trial number	Target	Phase	Enrollment	Primary endpoint	Overall status
Targeted therapy	Tivozanib	NCT01835223	VEGFR	Ib/II	33	PFS	Completed
	Apatinib	NCT02329860	VEGFR-2	III	400	OS	Completed
	Anlotinib	NCT02809534	VEGFR, FGFR, PDGFR, c-Kit	II	50	PFR	Completed
	Fruquintinib	NCT06446154	VEGFR	II	36	ORR	Recruiting
	Chiauranib	NCT03245190	VEGFR/Aurora B/CSF-1R	Ib	27	PFR	Completed
	Tepotinib	NCT01988493	c-Met	Ib/II	117	TTP	Completed
	Cabozantinib	NCT04767906	VEGFR, c-Met, AXL	II	16	TT	Completed
	Cabozantinib+sapanisertib	NCT06811116	VEGFR, c-Met, AXL, mTOR	I/II	92	DLTs, AEs, PFS	Recruiting
	Trametinib+sorafenib	NCT02292173	MEK, VEGFR, Raf, PDGFR	Ia/Ib	17	MTD	Completed
	Temsirolimus+sorafenib	NCT01687673	mTOR, VEGFR, Raf, PDGFR	II	29	TTP	Completed
Immunotherapy	Pembrolizumab	NCT03062358	PD-1	III	453	OS	Completed
	Camrelizumab	NCT02989922	PD-1	II	220	ORR, OS rate	Completed
	Tislelizumab	NCT03412773	PD-1	III	674	OS	Completed
	Nivolumab	NCT02576509	PD-1	III	743	OS	Completed
	Nivolumab+ipilimumab	NCT04039607	PD-1, CTLA-4	III	732	OS	Active, not recruiting
	HBV-TCR-T	NCT04677088	HBV antigens	I	7	AEs, SAEs	Completed
	GPC3 CAR-T (CBG166)	NCT06461624	GPC3	I	15	DLTs, AEs, MTD	Recruiting
	CAR-NK (SN301A)	NCT06652243	GPC3	I	12	DLTs, AEs, SAEs	Recruiting
	Autologous NK	NCT06044506	/	I	3	OTD	Recruiting
	TIL therapy (BST02)	NCT06526832	/	I	9	AEs, SAEs, DLTs, MTD	Recruiting
Immunotherapy combined with targeted therapy	TACE+atezolizumab+bevacizumab	NCT04712643	PD-L1, VEGF	III	342	PFS, OS	Active, not recruiting
	Anlotinib+penpulimab	NCT04344158	PD-1, VEGFR, FGFR, PDGFR, c-Kit	III	649	OS	Active, not recruiting
	Sintilimab+bevacizumab biosimilar (IBI305)	NCT03794440	PD-1, VEGF	II-III	595	PFS, OS	Completed
	Camrelizumab+rivoceranib	NCT03764293	PD-1, VEGFR2	III	543	PFS, OS	Completed
	Toripalimab+bevacizumab	NCT04723004	PD-1, VEGF	III	326	PFS, OS	Completed
	TACE+durvalumab+bevacizumab	NCT03778957	PD-L1, VEGF	III	724	PFS	Active, not recruiting
	KN046+lenvatinib	NCT04542837	PD-L1, CTLA-4, VEGFR, FGFR	II	55	ORR	Completed

HCC, hepatocellular carcinoma; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; c-Kit, cellular proto-oncogene tyrosine-protein kinase Kit; FGFR, fibroblast growth factor receptor; Aurora B, aurora kinase B; CSF-1R, colony-stimulating factor 1 receptor; AXL, axl receptor tyrosine kinase; HIF1α, hypoxia-inducible factor 1 α; c-Met, hepatocyte growth factor receptor; Raf, rapidly accelerated fibrosarcoma; TACE, transarterial chemoembolization; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; HBV, hepatitis B virus; GPC3, glypican-3; TCR-T, T cell receptor-engineered T cell; CAR-T, chimeric antigen receptor T cell; NK, natural killer cell; TIL, tumor-infiltrating lymphocyte; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; PFR, progression-free rate; TTP, time to progression; TT, time on treatment; DLTs, dose-limiting toxicities; AEs, adverse events; MTD, maximum tolerated dose; OTD, optimal treatment dosage; SAEs, serious adverse events.

to PD-1/CD80 to unleash T-cell suppression and restore anti-tumor immunity, while bevacizumab inhibits tumor angiogenesis (blocking nutrient supply) and repels VEGF-mediated immunosuppression in the TME to enhance T-cell infiltration. Their combination exerts a dual effect of "relieving immunosuppression + improving immune microenvironment". Phase III IMbrave150 trial results confirmed its significant advantages: in treatment-naive patients with unresectable HCC, the combination reduced death risk by 42%, with a 12-month OS rate of 67.2% (vs. 54.6% in the sorafenib group) [267]. This regimen is the first to verify the OS benefit of the "immuno + anti-angiogenesis" strategy in first-line settings. As the new standard treatment for Child-Pugh Class A patients, this combination proves effective for high-risk groups. Marking an era advancing from "targeted monotherapy" to "immune combination", this combination reshapes the current first-line treatment, and lays the groundwork for future immune treatment optimization. In addition, the phase III clinical trials of toripalimab combined with bevacizumab and durvalumab combined with bevacizumab have also harvested encouraging outcomes [268]. These trials provide multiple options for the clinical treatment of HCC, as well as inspirations for future research.

Sintilimab combined with bevacizumab biosimilar (IBI305), versus sorafenib, has exhibited marked benefits to progression-free survival (PFS) and OS with a good safety, and the combination of sintilimab with apatinib plus capecitabine also exhibits favorable anti-tumor activity [269,270]. Pembrolizumab has proven effective in post-sorafenib patients [271]. Moreover, the effect of pembrolizumab as a combination agent cannot be ignored. Studies have shown that transarterial chemoembolization (TACE) combined with lenvatinib and pembrolizumab can extend the PFS [272]. Additionally, a multicenter trial found that compared with sorafenib, anlotinib plus pembrolizumab significantly prolongs the median OS [273]. Camrelizumab-based regimens, including triple therapies with lenvatinib+raloxifene-based hepatic arterial infusion chemotherapy (HAIC), shows a significant anti-tumor activity and a well-tolerated profile [274]. In a phase II study, the combined treatment of camrelizumab, apatinib, and HAIC achieves a good efficacy in specific HCC patients [275]. Furthermore, in a multicenter study, camrelizumab combined with rivoceranib displays an evident efficacy [276]. Tislelizumab, another immunotherapeutic agent, does not show a significant effect, but a higher safety profile than sorafenib [277]. In addition, nivolumab and ipilimumab have also been written into guidelines. In a phase III trial, the combination of nivolumab and ipilimumab significantly improves the OS, compared with the control group [278].

In addition to ICIs, cellular immunotherapy has emerged to counter HCC. T cell receptor-engineered T cells (TCR-T) therapy can be designed by engineering the patient's own T cells. Relevant studies have shown that HBV-TCR-T therapy is safe and tolerant, and some patients have experienced long-term disease-free survival [279]. In patients with HBV-related HCC recurrence after liver transplantation, multiple infusions of mRNA-electroporated HBV-specific TCR-T cells are well-tolerated [280]. Chimeric antigen receptor T cell (CAR-T) therapy has been introduced into the treatment of gastric cancer, but the evidence about HCC is still under exploration. Moreover, CAR-NK therapy has been set up. Glypican-3 (GPC3)-specific NK cells exhibit a significant toxicity against GPC3-positive HCC *in vitro*, with a stable activity under hypoxic conditions and a remarkable anti-tumor effect in xenograft models [281]. Furthermore, tumor-infiltrating lymphocyte (TIL) therapy is designed through isolating and expanding tumor-reactive T cells from the patient's tumor tissue and then infusing them back into the patient. This therapy, such as drug BST02 injection, overcomes the TME barrier, but its application is still in the early explorational stage.

Bispecific therapy refers to a class of therapeutics specially designed to simultaneously target two distinct biomolecules. Currently, bispecific antibodies represent its primary form, among which KN046 is a relatively well-developed candidate. As an anti-PD-L1/CTLA-4 bispecific antibody, KN046 in combination with lenvatinib has achieved an objective response rate (ORR) of 45.5%, thereby providing a promising first-line treatment option for patients with advanced HCC [282].

6.3 Predictive Biomarkers for Therapy Response

Although the aforementioned therapies have transformed the HCC treatment landscape, their efficacy remains limited in patients presenting a heterogeneity, or having developed primary or acquired resistance. Therefore, predictive biomarkers should be explored to personalize treatments. The immune cell infiltration in the TME is directly related to the therapeutic efficacy. Based on the degree of functional immune cell infiltration, particularly $CD8^+$ T cells, tumors can be classified as "cold" or "hot", with hot tumors more responsive to immunotherapy [283]. A high intratumoral immune infiltration predicts a better response to immunotherapy and a favorable prognosis [284].

Moreover, the activation of β-catenin, often driven by mutations in the *CTNNB1* gene, may create an "immune desert" phenotype, in which the efficacy of ICIs is offset, ending up with an unsatisfactory immunotherapeutic response [285,286]. Furthermore, tumor mutational burden (TMB) can predict the efficacy of immunotherapy in various cancers, as a high TMB implies more neoantigens and a stronger immunogenicity [287]. However, the predictive power of TMB varies with the type of cancer and the status of the TIME [288]. The TCGA cohort shows that the burden of non-synonymous mutations is not high in HCC,

Table 4. Key mechanisms of drug resistance in HCC.

Category	Mechanism	Related pathways/cells	Description
Cellular intrinsic mechanisms	Pathway compensation and reactivation	ERK, Akt, c-Met, EGFR, TGF-β, Hh	Compensatory activation of alternative pathways in response to single-pathway targeted therapy
	Drug efflux	ABC transporter	Drug efflux mediated by ABC transporters, leading to a reduction in intracellular drug concentration
	Metabolic reprogramming	OXPHOS	A metabolic shift towards OXPHOS-based survival, rendering certain HCC subtypes insensitive to glycolysis inhibitors
TME-mediated mechanisms	Immune evasion	PD-L1, Tregs, M2-TAMs, MDSCs, Texs	Immunosuppression leading to severe T cell exhaustion and impaired function, resulting in immunotherapy failure
	Hypoxia	HIF	Anti-angiogenesis therapy induced hypoxia activates the HIF pathway, leading to enhanced tolerance to an anoxic microenvironment

HCC, hepatocellular carcinoma; ERK, extracellular signal-regulated kinase; Akt, protein kinase B; c-Met, hepatocyte growth factor receptor; EGFR, epidermal growth factor receptor; TGF-β, transforming growth factor-β; Hh, Hedgehog; ABC, ATP-binding cassette; OXPHOS, oxidative phosphorylation; TME, tumor microenvironment; PD-L1, programmed death-ligand 1; Tregs, regulatory T cells; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; Texs, exhausted T cells; HIF, hypoxia-inducible factor.

which limits the predictive value of TMB. Therefore, multiple biomarkers should be integrated to predict the response and prognosis [289].

6.4 Drug Resistance

Although significant progress has been made in HCC diagnostics and therapy, patient outcomes remain poor. This is primarily attributed to primary resistance caused by intratumor heterogeneity and acquired resistance that arises from the tumor's adaptation to therapeutic pressure [290]. Further investigation into drug resistance mechanisms provides key insights into the factors driving treatment failure in HCC patients and offers guidance for developing more effective combination therapies. The major mechanisms of drug resistance in HCC are summarized in Table 4.

7. Conclusions and Future Prospects

In a majority of cases, HCC develops with the long-term progression of chronic liver disease. The liver microenvironment demonstrates dynamic changes as chronic hepatitis aggravates to cirrhosis, including inflammatory cell infiltration, activation of HSCs, deposition of extracellular matrix, and gradual accumulation of immunosuppressive cells, collectively laying the soil for the growth of HCC. Some signaling pathways may dominate in one stage, but also continue to function in other stages. The inflammatory pathway NF-κB pathway runs throughout all the processes to HCC, linking liver injury to carcinogenesis, while the fibrotic pathway TGF-β pathway mainly drives fibrosis prior to carcinogenesis. During the HCC stage, the signaling pathways are primarily responsible for cell proliferation and immunosuppression. We specifically elaborate on the abnormal activation of key signaling pathways in the HCC TME, including RTK, ERK, Wnt/β-catenin, TGF-β, PI3K/AKT/mTOR, Hh, NF-κB, and HIF pathways. Through complex crosstalk and feedback loops, these pathways collectively build up a highly immunosuppressive microenvironment that favors tumor progression and treatment resistance. Our review is limited in not providing a detailed discussion on the multilevel regulatory networks among these pathways, as well as how these complex networks synergistically or antagonistically decide the fate of HCC.

Targeting TME components and their aberrantly activated signaling pathways has become a crucial strategy for current HCC treatment. The progression from multikinase inhibitors targeting RTKs to ICIs highlights the effectiveness of intervening in the HCC TME. But these treatments are also confronted with the high heterogeneity of tumors, the complexity of the TME, and the acquired drug resistance. Sensitive biomarkers will help guide the creation of individualized therapy. Extensive crosstalk and compensatory activation among signaling pathways often lead to resistance against single-pathway targeted therapies. Thus, combination therapies will remain the mainstream to combat drug resistance. Furthermore, cell therapies, RNA interference therapeutics, and nanodrug delivery systems will offer new treatment options. Future research should dig deeper into the TME complexity for deciphering the molecules capable of preventing resistance and immune evasion, as well as reversing the pro-tumorigenic microenvironment.

New analytical tools can be utilized to gain a clearer insight into the evolution of the HCC TME. Through spatial transcriptomic analysis, gene expression can be integrated with spatial information to construct the maps of functional genes within tissues [291]. The combination of spatial transcriptomics and single-cell sequencing en-

ables a deeper elucidation of the mechanisms underlying the interactions between cancer cells and other cell types in tumor tissues [21]. Multi-omics integration analysis allows to synthesize multidimensional biological processes to investigate the mechanisms of cancer initiation, and facilitate the early screening, exploration of therapeutic targets, and discovery of biomarkers [292]. Additionally, patient-derived organoid models are capable of mimicking the structure and function of tumors *in vivo*, thereby offering sparks for designing new personalized therapy and precision medicine [293]. Finally, liquid biopsy biomarkers, such as methylated cell-free DNA and miRNAs in exosomes, have promise a high value in the diagnosis and dynamic monitoring of HCC, thus enabling real-time identification of the therapeutic window [294,295]. In conclusion, these emerging tools are expected to provide more information about the dynamics in HCC TME, which may be exploited to realize the early detection and precise treatment of HCC.

Author Contributions

LX and XZhang designed, wrote and revised the manuscript. LX and XZhu prepared figures of the manuscript. XZhang and DN contributed to making table of the manuscript. LX and XZhang participated in collecting data of the manuscript. HZ and CJ participated in the conception and design of the review, undertook significant revisions to optimize the academic content, and completed thorough proofreading of the manuscript. CJ also provided support for the publication of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used DeepSeek in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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