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Targeted therapy for hepatocellular carcinoma: Challenges and opportunities

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, which ranks as the sixth of cancer-related death. Despite the emergence of targeted therapy, advanced-stage HCC remains largely incurable due to low response rate and therapeutic resistance. In this review, we mainly focused on the current progression of multi-kinase inhibitors and immunotherapies in the treatment of HCC. We highlight the mechanism underlying the ineffectiveness of these targeted therapies, including oncogenic alterations in driver genes and downstream pathways, high heterogeneity of HCC, and the mutual interaction of tumor microenvironment that promotes therapeutic resistance. We also discussed how these previous studies suggested for future therapeutic strategies. Besides, the complexity of HCC heterogeneity and cancer revolution need to be recognized in personalized therapy. Establishment of a drug screening system and identification of biomarkers of response is also in urgent need to overcome drug resistance. Meanwhile, a combination of targeted therapies could also be explored as a promising strategy in the future.

1. Introduction

Liver cancer is the sixth most commonly diagnosed cancer, with about 841,000 newly diagnosed cases and 782,000 deaths annually [1]. Hepatocellular carcinoma (HCC), accounting for about 80% of primary liver cancer, is the major pathological type. According to CONCORD-3 data reported by the *Lancet*, for most cancers, the survival trends are generally increasing due to the access to early diagnosis and optimal treatment. However, in most countries, liver cancer survival has changed very little during the 20-year period (1995–2014). The five-year net survival rate of liver cancer was in the range of 5–30% throughout 2000–2014. Take China for an example, the survival rate was 11.7% during 2000–2004, only increased to 14.1% during 2010–2014 [2]. In fact, the majority of HCC patients are diagnosed in advanced-stage, at which point surgical treatments (resection and transplantation) and locoregional treatment (chemoembolization) have been disappointing in terms of patients' overall survival [3]. Meanwhile, traditional chemotherapies, such as 5-fluorouracil, cisplatin, doxorubicin, or gemcitabine, haven't shown promising outcomes. Therefore, the development of effective targeted therapy for advanced HCC is in urgent need.

In 2007, a multi-kinase inhibitor (MKIs), sorafenib, was approved as the first systemic agent for the treatment of advanced unresectable HCC as Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial had suggested a survival benefit of about 3 months [4]. Since then, a glimmer of hope for unresectable advanced

Abbreviations: HCC, hepatocellular carcinoma; MKI, multikinase inhibitor; FDA, Food and Drug Administration; ORR, objective response rate; OS, overall survival; EGF, epidermal growth factor; LPC, liver progenitor cells; TICs, tumor-initiating stem-like cells; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; SCF, stem cell factor; c-KIT, also known as CD117; GFRα, growth factor alfa; HGF, hepatocyte growth factor; JAK, janus kinase; NF-κB, nuclear factor kappa-B; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; TANs, Tumor-associated neutrophils; TICs, tumor initiating cells; LPCs, liver progenitor cells; GPC3, glypican-3; PD-1, programmed cell death 1; CAR-T, chimeric antigen receptor-modified T cells; TMB, tumor mutational burden; CXCR4, cell-derived 1 alpha receptor

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HCC has attracted various clinical trials testing for candidate targeted drugs. Currently, three oral multi-kinase inhibitors, sorafenib, regorafenib and lenvatinib, have been approved as first-line or second-line therapy for advanced HCC [5]. For immunotherapy, an anti-PD-1 monoclonal antibody, Nivolumab, has been granted accelerated approval from Food and Drug Administration (FDA) to treat advanced HCC based on promising results from a phase II trial (Checkmate-040) [6]. Also, other targeted therapies, such as GPC3 based CAR-T and AMPK inhibitors are also under exploration [7,8].

Despite those promising data in clinical trials, targeted therapies still confronted with problems like low objective response rate (ORR) and adaptive or acquired resistance [4,9–11]. These unsatisfied outcomes mainly result from heterogeneity of HCC derived from its morphological diversity, signal transduction network and microenvironmental discrepancies *etc* [12,13]. Thus, researches on biomarkers of liver cancer classification, biomarkers of response and how to deal with cancer revolution within tumors during therapy are still expected. In this review, we summarized the recent targeted therapies for HCC, mechanisms on resistance and potential strategies to overcome low efficacy of current therapies, in hope of shedding light on precision medicine for HCC in future researches.

2. Multi-kinase inhibitors

2.1. Introduction of multi-kinase inhibitors

Sorafenib, an oral multikinase inhibitor (MKI), which blocks tyrosine kinase receptor (VEGFR-2/3, PDGFR-β, c-Kit, FLT-3, RET), downstream pathway kinase (Ras/Raf/MEK/ERK, JAK/STAT) activities and other targets (c-Raf, B-Raf), is the first approved systemic agent for advanced liver cancer (Fig. 1) [14–16]. According to SHARP trial, sorafenib showed a 2.8-month prolonged survival for patients compared with the placebo group, with a median overall survival (OS) of 10.7 months versus 7.9 months. This trial offered a standard trial framework for assessing promising agents. However, the past decade (2008–2017) has witnessed several failed phase III trials followed the SHARP trial (sunitinib in 2013 [17], brivanib in 2013 [18], sorafenib plus erlotinib in 2015 [19], linifanib in 2015 [20]) until the advent of two other oral MKIs, regorafenib and lenvatinib (See Table 1).

Regorafenib, similar to sorafenib in structure and function, was initially applied for metastatic colorectal cancer and gastric cancer [30,31]. Compared with sorafenib, it is predisposed to suppress VEGFR signaling and has a distinct anti-angiogenic effect [32]. Notably, the global trial (RESORCE, NCT01774344) demonstrated median survival improvement in patients who have received regorafenib after sorafenib treatment (median OS 10.6 months versus 7.8 months; HR 0.63, 95% CI 0.50–0.79; $p < 0.001$) [27]. This trial led to FDA approval for regorafenib as a second-line agent for HCC patients with sorafenib tolerance in April, 2017. Followed with the positive response of regorafenib, Lenvatinib, which broadly targets VEGFR 1–3, KIT, FGFR1-4, PDGFRα and SCFR showed non-inferiority to sorafenib in term of OS in Study 304/REFLECT [23], getting approved by FDA as a first-line treatment for advanced liver cancer in 2018 [33–36].

2.2. Mechanism of resistance

Though the successful breakthrough of multikinase inhibitors has brought hope to advanced HCC, the overall outcomes are far from

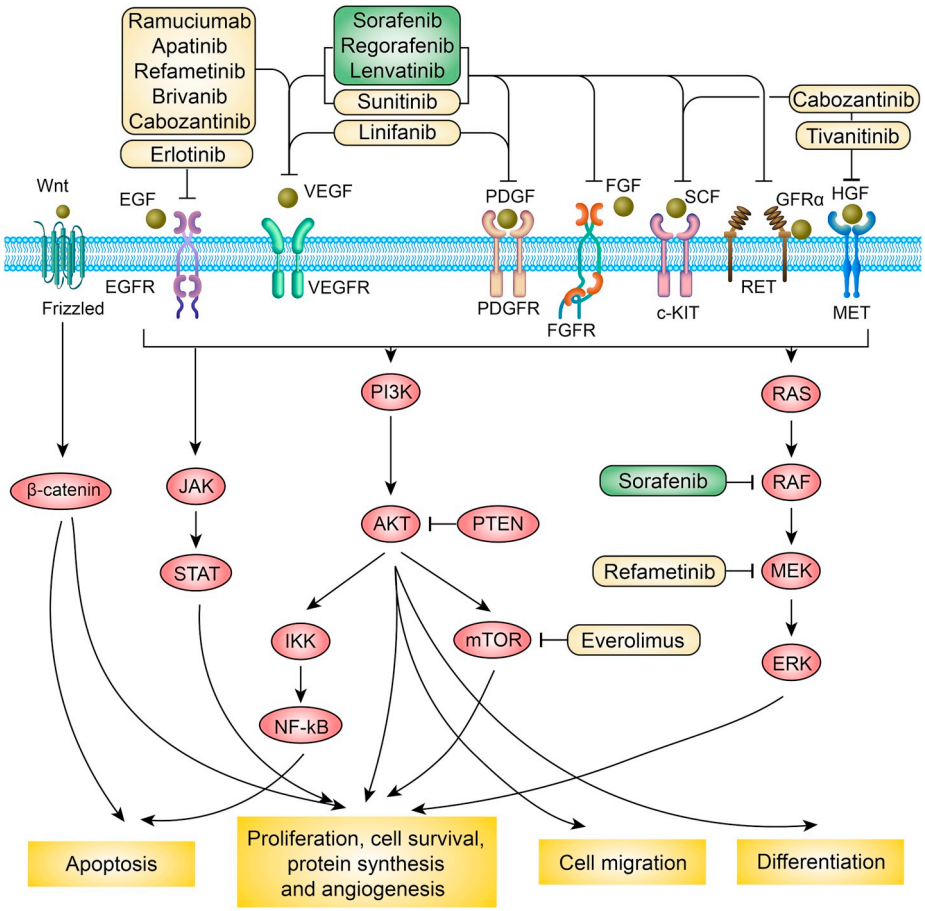

Fig. 1. Targeted therapies for HCC and their targeted signaling pathways: The diagram summarizes the approved (green) and potential (yellow) targeted agents under phase II or III clinical trials and their pathways involved in HCC progression.

Table 1
Clinical trials of MKIs in HCC.

	Study	Phase	Mechanism of action	Randomisation (n)	Median OS			Median TTP			ORR (%)	Referen-ces
					Months	p value	HR (95% CI)	Months	p value	HR (95% CI)		
First line												
sorafenib	SHARP (2008)	3	VEGFR, PDGFR, RAF, KIT	Sorafenib (n = 299) vs placebo (n = 303)	10.7 vs 7.9	< 0.001	0.69 (0.55–0.87)	5.5 vs 2.8	< 0.001	0.58 (0.45–0.74)	2 vs 1	[4]
sorafenib	Asia-Pacific region (2009)	3	VEGFR, PDGFR, RAF, KIT	Sorafenib (n = 150) vs placebo (n = 76)	6·5 vs 4·2	0·014	0·68 (0·50–0·93)	2·8 vs 1·4	0·0005	0·57 (0·42–0·79)	3.3 vs 1.3	[21]
Sunitinib	SUN1170 (2013)	3	KIT, FLT3, RET	Sunitinib (n = 530) vs sorafenib (n = 544)	7·9 vs 10·2	NS		4.1 vs 3.8	NS		6.6 vs 6.1	[17]
Brivanib	BRISK-FL (2013)	3	FGFR, VEGFR	Brivanib (n = 577) vs sorafenib (n = 578)	9·5 vs 9·9	NS		4·2 vs 4·1	NS		12 vs 9	[22]
Linifanib	LiGHT (2015)	3	VEGFR and PDGFR	Linifanib (n = 514) vs sorafenib (n = 521)	9·1 vs 9·8	NS		5·4 vs 4·0	0·001	0.76 (0.64–0.90)	13.0 vs 6.9	[20]
Erlotinib + sorafenib	SEARCH (2015)	3	EGFR	Erlotinib plus sorafenib (n = 362) vs sorafenib (n = 358)	9·5 vs 8·5	NS		3·2 vs 4·0	NS		6.6 VS 3.9	[19]
Lenvatinib	REFLECT/Study 304 (2017)	3	VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT	Lenvatinib (n = 478) vs sorafenib (n = 476)	13·6 vs 12·3	< 0·0001	0.92 (0.79–1.06)	8.9 vs 3.7	< 0·0001	0·60 (0·51–0·71)	40 vs 13	[23]
Second line												
Brivanib	BRISK-PS (2013)	3	FGFR, VEGFR	Brivanib (n = 263) vs placebo (n = 132)	9.4 vs 8.2	NS		4.2 vs 2.7	< 0.001	0.56 (0.42–0.76)	4.2 vs 2.7	[24]
Everolimus	EVOLVE-1 (2014)	3	mTOR	Everolimus (n = 362) vs Placebo (n = 184)	7.6 vs 7.3	NS		3.0 vs 2.6	NS		2.2 vs 1.6	[25]
Ramucirumab	REACH (2015)	3	VEGFR-2	Ramucirumab (n = 283) vs Placebo (n = 282)	9.2 vs 7.6	NS		3.5 vs 2.6	< 0.001	0.59 (0.49–0.72)	7 vs 1	[26]
Regorafenib	RESORCE (2017)	3	VEGFR, PDGFR, RAF, KIT	Regorafenib (n = 379) vs Placebo (n = 194)	10.6 vs 7.8	< 0.001	0.62 (0.50–0.78)	3.2 vs 1.5	< 0.001	0.44 (0.36–0.55)	11 vs 4	[27]
Axitinib	NCT01210495 (2015)	2	VEGFR 1–3	Axitinib (n = 134) vs Placebo (n = 68)	12.7 vs 9.7	NS		3.7 vs 1.9	0.006	0.621	9.7 vs 2.9	[28]
Tivantinib	NCT01755767 (2017)	3	MET	tivantinib (n = 226) vs placebo (n = 114)	8.4 vs 9.1	NS		2.4 vs 3.0	NS			[29]

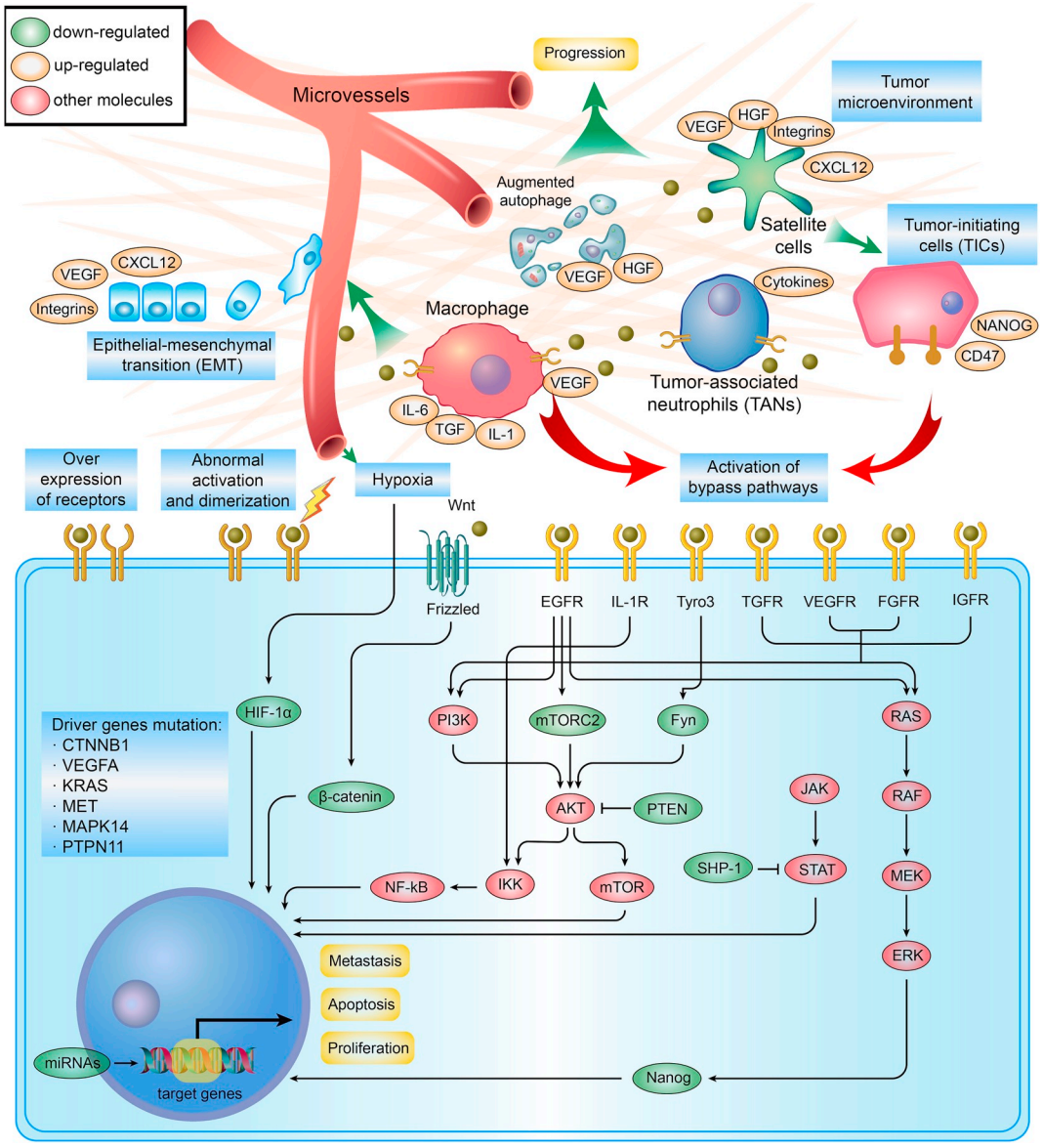

Fig. 2. Mechanisms underlying resistance of MKIs in HCC: The diagram depicts the potential mechanisms or pathways involved in drug resistance of HCC, mainly including ① altered signaling pathways (molecules in green are downregulated in pathways); ② driver genes and epigenetic modification; ③ tumor microenvironment; ④ cancer stem cells (CSCs) or tumor initiating cells (TICs). **Abbreviation**: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; SCF, stem cell factor; c-KIT, also known as CD117; GFRα, growth factor alfa; HGF, hepatocyte growth factor; JAK, janus kinase; NF-κB, nuclear factor kappa-B; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; IGFR, insulin-like growth factor receptor; TGF, transforming growth factor; IL, interleukin; TANs, tumor-associated neutrophils; CXCL12, C-X-C motif chemokine 12, also known as stromal cell-derived factor 1 (SDF1).

satisfactory. A large proportion of patients are not showing benefit from the therapy, reflecting in low ORR (mostly < 10%, sorafenib for 2–3%) and drug resistance. According to previous studies, both innate and acquired resistance are involved in sorafenib resistance. Among four potential mechanisms we discussed below, altered signaling pathways and driver gene mutations are related to both, while tumor microenvironment and cancer stem cells related resistance are mainly categorized as acquired resistance [37,38]. Investigating the mechanism of resistance is the key to develop new therapeutic strategies to overcome this bottleneck issue. Here we mainly summarized common mechanisms concerned with MKIs resistance in HCC (Fig. 2).

2.2.1. Altered signaling pathways

When epidermal growth factor (EGF) binding with corresponding ligands, epidermal growth factor receptor (EGFR), it can regulate many biological effects, including cell growth, proliferation, angiogenesis, and differentiation. EGFR mutation is presented in more than half of HCC patients, suggesting an oncogenic role of EGFR and a therapy value of its antagonists [39,40]. These constitutively active mutations of EGFR exert their function via activation of multiple oncogenic pathways, including MAPK, PI3K-AKT, and JAK signaling pathways [41]. Several MKIs haven't shown promising results in terms of survival improvement due to activated downstream signaling pathways involved in EGFR activation.

Recently, our lab has found that overexpression of choline kinase α could facilitate functional interaction between EGFR and mTORC2 for Akt activation, which promoted HCC metastasis and drug resistance of gefitinib and erlotinib [42]. In another cohort study, we reported that

HCC patients with low expression of Shp2 exhibited superior prognosis to sorafenib. Shp2 could amplify β-catenin signaling, which led to the enhanced self-renewal and expansion of liver cancer stem cells (CSCs) [43]. Accordingly, by down-regulation of it, the activation of Ras/Raf/Erk pathway and PI3K/Akt/mTOR cascade were blocked, resulting in enhanced sensitivity of HCC cells to sorafenib [44]. Consistent with the previous study, combining rapamycin or aspirin to disrupt the mTOR signaling pathway could potentiate the anti-cancer effect of sorafenib [45,46]. Other than Shp2, a novel LncRNA, THOR (testis-associated highly conserved oncogenic long non-coding RNA) was recently identified as an activator of downstream Wnt-catenin signaling pathway, which promoted self-renewal of liver CSCs, indicating that HCC patients with low THOR expression might benefit more from sorafenib treatment [47]. These studies imply to identify biomarkers for selecting patients who might benefit more from the systemic therapy. Also, combining therapies incorporating inhibitors of the downstream dysregulated signaling pathways is also an option.

2.2.2. Driver genes and resistance

There is no doubt that somatic genomic and epigenomic alterations accumulate to promote tumorigenesis. Whole-exome sequencing (WES) studies and single-nucleotide polymorphism (SNP) array analyses have detected dozens of mutations and “drivers” genes with high frequency which could be considered as HCC origin [48–50]. Studies revealed that these pivotal altered genes share pathways with MKIs, which could contribute to drug resistance.

Altered CTNNB1 is commonly found in HCC (23–36%) and is related to WNT–β-catenin signaling. Active CTNNB1 mutations are more common in hepatitis C virus (HCV)-related (more than half of HCV patients) compared with hepatitis B virus (HBV)-related HCC, associated with a particular WNT gene expression profile. Therefore, the subtypes of HCC patients and etiology may affect the efficacy of sorafenib [51,52].

VEGFA is another driver gene in HCC (frequency: 7–10%), mostly detected as copy number alterations. A study showed that high-level VEGFA amplification in HCC cells could lead to excessive production of hepatocyte growth factor (HGF), which induced cancer cell proliferation [53]. Notably, patients with VEGFA amplification responded better to sorafenib, suggesting that focal gains of VEGFA could serve as candidate predictor of sorafenib response in HCC [53,54]. IGF2 was mainly abnormally activated by epigenetic mechanisms including aberrant promoter methylation and miRNA de-regulation. Increased IGF2 expression has a strong association with VEGF expression, thus it may promote tumor progression through angiogenesis. Data also suggests that IGF1/2 mAbs may be a promising candidate for precision medicine [55].

KRAS (Kirsten rat sarcoma), an isoform of RAS, is a frequently mutated oncogene in most cancers, though the mutation rate in HCC is relatively low (about 1%). RAS proteins are common upstream mediators of major sorafenib targeted pathways—RAF/MAPK and PI3K/AKT/mTOR signaling axis [56–59]. A recent study has found that KRAS inhibition could markedly suppress RAF/ERK and PI3K/AKT signaling *in vitro* and *in vivo*. This study further demonstrated that the combination of KRAS inhibition and sorafenib treatment revealed synergistic anti-tumoral effect in HCC. Accordingly, in sorafenib-resistant HCC cells with elevated KRAS expression, KRAS inhibition could resensitize the efficacy of sorafenib, indicating that additional inhibition of KRAS might be a potential therapeutic strategy for this subtype of HCC [60].

Other than the above frequent mutated driver genes of HCC, Rudalska R et al. conducted an *in vivo* RNAi screening to identify genes likely to be involved in sorafenib resistance [61]. They identified Mapk14 (p38α) as a candidate gene by using a pooled shRNA screening. Further studies demonstrated that silencing Mapk14 could sensitize mouse HCC to sorafenib treatment by activation of Mek-Erk and Atf2 signaling. This study suggested a combination of sorafenib and Mapk14 blockade as a promising approach to overcoming therapy resistance of human HCC.

2.2.3. Tumor microenvironment and resistance

Tumor microenvironment consists of a complex mixture of several types of non-malignant cells, extracellular matrix, and signaling molecules, playing a key role in both tumor progression and the response to therapies via inducing inflammation, angiogenesis, hypoxia and fibrosis, especial in chronically damaged liver tissue [62–64]. Cytokines such as interleukin-1 and 6 (IL-1 and IL-6, respectively) after the activation of liver-resident macrophages (Kuffer cells) and inflammatory cells interacted with extracellular matrix to facilitate liver cancer fibrosis and carcinogenesis.

The disappointing results of multi-kinase inhibitors in clinical trials have led to the exploration of varied roles of EGFR in different cell types of liver other than hepatocyte. In 2014, Hanane Lanaya et al. has reported that lacking EGFR in macrophages impaired hepatocarcinogenesis, whereas hepatocytes deprived of EGFR developed more tumors, suggesting diversed roles in mesenchymal cells and hepatocyte. By employing mice models with EGFR knockout in different cell types, this study further demonstrated that EGFR is indispensable in liver macrophages to induce IL-6 secretion, followed with the activation of downstream pathways. The finding of the tumor-promoting mechanism for EGFR in non-tumor cells could lead to more effective precision strategies in guiding MKIs treatment [65].

Tumor-associated neutrophils (TANs) could interact with the tumor microenvironment via the release of cytokines, which might in return regulate the recruitment of TANs [66]. It has been reported that sorafenib treatment could increase TANs infiltration via HIF-α/NF-κB pathway, resulting in intratumoral infiltration of macrophages and Treg cells to promote HCC progression. Accordingly, TANs infiltration is correlated with response to sorafenib in HCC patients. The study also demonstrated that TANs depletion combined with sorafenib treatment inhibited tumor growth and angiogenesis.

Hypoxia is commonly found within tumors due to the massive oxygen need for expansion. Moreover, HIF-1α regulates a serious of genes related to glucose metabolism and proliferation. Our team has found that erythrocytosis in HCC induced by dysregulation of HIF-1α portended poor prognosis [67]. Sorafenib was supposed to inhibit HIF-1α synthesis as an implication for antiangiogenic activity [68]. When autophagic degradation of HIF-1αwas inhibited by ADRB2 signaling, the anti-tumor activity of sorafenib was impeded [69]. However, several studies also indicated that sustained sorafenib treatment could further induce hypoxia, activating HIF-1α induced VEGF pathway, consequently leading to tumor angiogenesis [66,70]. A combination of sorafenib and HIF-1α inhibition (EF24, adrenoceptor antagonist *etc.*) showed a synergetic effect against tumor cell growth [69,70]. In some cases, hypoxia response could switch from HIF-1α to HIF-2α dependent pathway, activating TGF-α/EGFR pathway, which indicated targeting HIF-2α could also be a potential way to enhance sorafenib efficacy [71].

2.2.4. Cancer stem cells and resistance

Many solid tumors, including HCC, contain a small population of highly malignant cells which could differentiate into mature cancer cells, termed as tumor initiating cells (TICs) or CSCs. Growing evidence confirmed that TICs play a crucial role in tumorigenesis, dedifferentiation, malignant progression and resistance to chemotherapy [71]. The underlying mechanisms were investigated in several researches.

A study showed that liver progenitor cells (LPCs, cytokeratin 19/Oval cell 6-positive) could convert to liver CSCs under chronic inflammation. Clinical investigation revealed a superior response to sorafenib response in liver cancer patients with LPC-derived liver cancer [72]. Nanog is also considered a biomarker for CSCs in HCC, which could maintain the self-renewal of CSCs through IGF1R-signaling pathway. Therefore, Nanog-positive CSCs displayed a high ability of invasion and lower sensitivity to sorafenib administration [73]. In HCV-

related HCC, TLR4/NANOG oncogenic pathway is linked to suppression of TGF-β signaling [74]. A recent study reported a metabolic reprogramming role of NANOG via tumorigenic changes in oxidative phosphorylation and fatty acid metabolism, reducing its susceptibility to sorafenib [75]. Taken together, these studies indicated that CSC markers should be taken into consideration as a therapeutic indicator when evaluating sorafenib response. Besides the above CSCs biomarkers, molecules and non-coding RNAs involved in regulating CSCs expansion could also be used to predict the response of MKIs, such as Shp2, LncARSR and LncTHOR *etc*. [43,47,76].

2.3. Strategies to overcome MKIs resistance

To overcome the initial low response rate and avoid innate resistance of MKIs, the heterogeneity between each individual and intratumor heterogeneity should be taken into consideration when making agents selection for a certain patient. High-throughput gene sequencing and multi-omics technology facilitate researchers to have a whole picture of the genetic background and phenotype of a patient, which could help avoid predictable resistance.

The identification of biomarkers of response is another way to help make therapeutic strategies. Regorafenib was reported to increase the overall survival of HCC patients in a phase III trial (RESORCE) [27]. The subsequent research has analyzed plasma and tumor samples from participants and identified expression patterns of plasmic proteins and miRNAs that associated with response to regorafenib [77]. A number of studies have suggested different biomarkers to predict the response to MKIs in treating HCC, such as stem cell markers and Vessels That Encapsulate Tumor Clusters (VETC) [78,79]. However, their value in guiding the selection of therapy needs to be further tested.

Furthermore, patient-derived models could also be used for drug screening and monitoring tumor cell evolution during MKIs treatment to avoid possible acquired resistance. For example, liver cancer organoids which maintained the features of the parental tumors could be cultured *in vitro* for a long term. The liver cancer-derived organoids recapitulated the expression profiles of the corresponding tissue-of-origin provides a feasible model for testing drug sensitivities and guide sequential therapy [80].

Moreover, according to the research of the Cancer Genome Atlas PanCancer study, researchers proposed a new notion to identify a tumor based on its molecular alterations other than the traditional anatomic classification. Therefore, a therapeutic strategy that benefits in one tumor could possibly be used in patients with a similar molecule alternation pattern and genetic mutation profile [81–83]. In this way, by using integrative classification to identify cell-of-origin patterns of a tumor, the spectrum of therapy selection for liver cancer patients might be expanded.

3. Immunotherapies

3.1. CAR-T

Cancer immunotherapy is named as Breakthroughs of the Year by Science in 2013 due to the progress made in two fields: chimeric antigen receptor (CAR)-modified T cells and checkpoint inhibitors. CAR-T have been heralded as a promising technology due to the substantial benefit observed in patients with relapsed or refractory B-cell malignancies [84–87]. The success of CAR-T has encouraged many resources worldwide to recognize additional tumor-associated antigens aiming to extend the success to solid tumors. More than 200 CAR-T clinical trials are undergoing so far, with one third for solid tumor exploration (ClinicalTrials.gov). Among the most studied CAR-T trials, therapies for glioblastoma or neuroblastoma have the most target antigens.

In HCC, the possibility of directing T cells to recognize Glypican-3 (GPC3) was the most explored (NCT02905188). GPC3 was detected in 72% of HCC patients, but undetectable in normal hepatocytes, cirrhotic liver or benign liver diseases, which makes it a suitable candidate as a target antigen [88]. The administration of GPC3-derived antibody or peptide vaccine in treating HCC has been attempted as a therapeutic strategy, however, clinical trials of these agents didn't show promising results [89–92]. T cells with CARs or high-affinity T cell receptors targeting GPC3 were then engineered to recognize and destroy GPC3 positive human HCCs. In 2014, Li and his colleagues have observed prolonged survival of mice bearing HCC xenografts by the treatment of the third generation GPC3-treated CAR T cells *in vivo* [8]. They further developed T cells carrying two complementary CARs against GPC3 and a liver tissue-specific protein - asialoglycoprotein receptor1 (ASGR1), which could reduce the risk of on-target off-tumor toxicity while maintaining relatively potent anti-tumor efficacy [93]. In a recent study, to overcome the immune evasion mediated by the interaction of programmed cell death 1(PD-1) and PD-L1 T cells, GPC3-specific CAR-T cells carrying the PD-1-CH3 fusion protein were constructed, showing promise as a treatment for patients with HCC [94]. Despite the promising results of GPC-3 specific CAR-T in different studies, whether it could be approved as a novel therapy for HCC still needs to be further tested in clinical trials in a long run.

3.2. Anti-PD-1/L1

Programmed cell death 1(PD-1) is an immune coinhibitory receptor expressed on immune cells such as T cells, B cells, and natural killer (NK) cells. Upon the interaction with its ligand PD-L1, PD-1 could suppress antigen-specific T cell activation to negatively regulate its function. There are five anti-PD-1/L1 antibodies approved by the U.S. FDA in clinical practice, which are Nivolumab, Pembrolizumab for anti-PD-1and Atezolizumab, Avelumab and Durvalumab for anti-PD-L1 [95]. Nivolumab is the only anti-PD-1/L1 antibody approved for the treatment of patients with HCC on September 23, 2017 [96]. In CheckMate040, Nivolumab has shown a manageable safety profile and durable objective responses in patients with advanced HCC, which accelerated its approval [6]. Although its complete or partial response rate was approximately 20%, the efficacy is still more promising than the previous systemic agents.

Like MKIs, anti-PD-1/L1 therapy was also confronted with the concern of the selection of candidate patients and overcome resistance. The possibility of using the expression of PD-L1 in cancer cells as a biomarker to identify patients who might be most likely to benefit from the therapy was explored [97,98]. A recent study has revealed the potential application of exosomal PD-L1 expression as a predictor for anti-PD-1 therapy by evaluating the magnitudes of the increase of circulating exosomal PD-L1 during the early stage of treatment [99]. Other than the expression of PD-1, tumor mutational burden (TMB) identified as the total number of mutations per coding area of a tumor genome, is also suggested as a biomarker of response rate to PD-1 inhibition, with a correlation coefficient of 0.74, indicating that 55% of the differences in response rate across 27 included cancer types could be explained by TMB [100]. Since the response rate of Nivolumab in HCC is only moderate, how to predict the benefit of the therapy is still under exploration to guide the selection of patients.

In order to improve anti-PD-1/L1 blockade efficacy, a combination of therapies is investigated. One option might be anti-PD-1 in conjunction with another checkpoint inhibitor—anti-CTLA4 inhibitor. A clinical trial evaluating the combination of durvalumab (anti-PD-1/L1) and tremelimumab (anti-CTLA4) is undergoing. Based on promising data in other tumors, combination therapies with MKIs, other targeted agents (TGF-beta inhibitor, Hsp90 inhibitor *etc*.) and locoregional therapies (TACE *etc*.) are also under clinical trials in HCC patients [101]. A study also showed that when anti-PD-1 treatment was used with sorafenib, its anti-tumor immune response could be facilitated with CXCR4 (cell-derived 1 alpha receptor) inhibition in the tumor microenvironment [102]. Blocking TREM-1$^+$ tumor-associated macrophages also reversed anti-PD-L1 resistance in HCC [103]. Also,

inhibition of SIRPa in dendritic cells could potentiate antitumor immunity [104]. With anti-PD-1/L1 blockade serving as the backbone of a number of combination therapies, the results of these clinical trials are to be expected.

4. Perspectives

The development of HCC is a multistep process with a complex interaction of altered signaling pathways, tumor microenvironment, and varied genetic background, leading to high tumoral heterogeneity, which posed a great challenge to precision medicine. With the advancement in multi-omics and gene editing technology, precision medicine has brought hope to the previous “uncurable” patients. However, it's undeniable that we have faced with many bottleneck issues followed with the approval of the new drugs such as the unsatisfactory response rate, drug resistance, and immune escape *etc*. To overcome these issues, a thorough understanding of the molecular mechanism underlying tumoral heterogeneity is needed. Based on the identification of predictors for response and drug screening system for each individual to foresee tumor evolution, the tailored therapy of MKIs are expected to present more promising results with longer overall survival of patients. In addition, a combination of MKIs and immunotherapies or combination therapies incorporating inhibitors of multiple downstream pathways could also be a potential direction for designing clinical trials. Hopefully, with the efforts of government, doctors, and researchers, a standardized system could be established to screen patients, monitor and evaluate the efficacy of each therapy, taking a step further to the new era of precision medicine.Acknowledgment

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Conflicts of interest

The authors have no conflict of interest to disclose.

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