

# Potential Treatment Strategies for Hepatocellular Carcinoma Cell Sensitization to Sorafenib

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**Abstract:** Liver cancer is highly malignant, has a low sensitivity to chemotherapy, and is associated with poor patient prognosis. The last 3 years have seen the emergence of promising targeted therapies for the treatment of hepatocellular carcinoma (HCC). For over 10 years, before the discovery of lenvatinib, sorafenib was only first-line therapeutic agent available for the treatment of advanced HCC. However, several clinical studies have shown that a considerable proportion liver cancer patients are insensitive to sorafenib. Very few patients actually substantially benefit from treatment with sorafenib, and the overall efficacy of the drug has not been satisfactory; therefore, sorafenib has attracted considerable research attention. This study, which is based on previous studies and reports, reviews the potential mechanisms underlying sorafenib resistance and summarizes combination therapies and potential drugs that can be used to sensitize HCC cells to sorafenib.

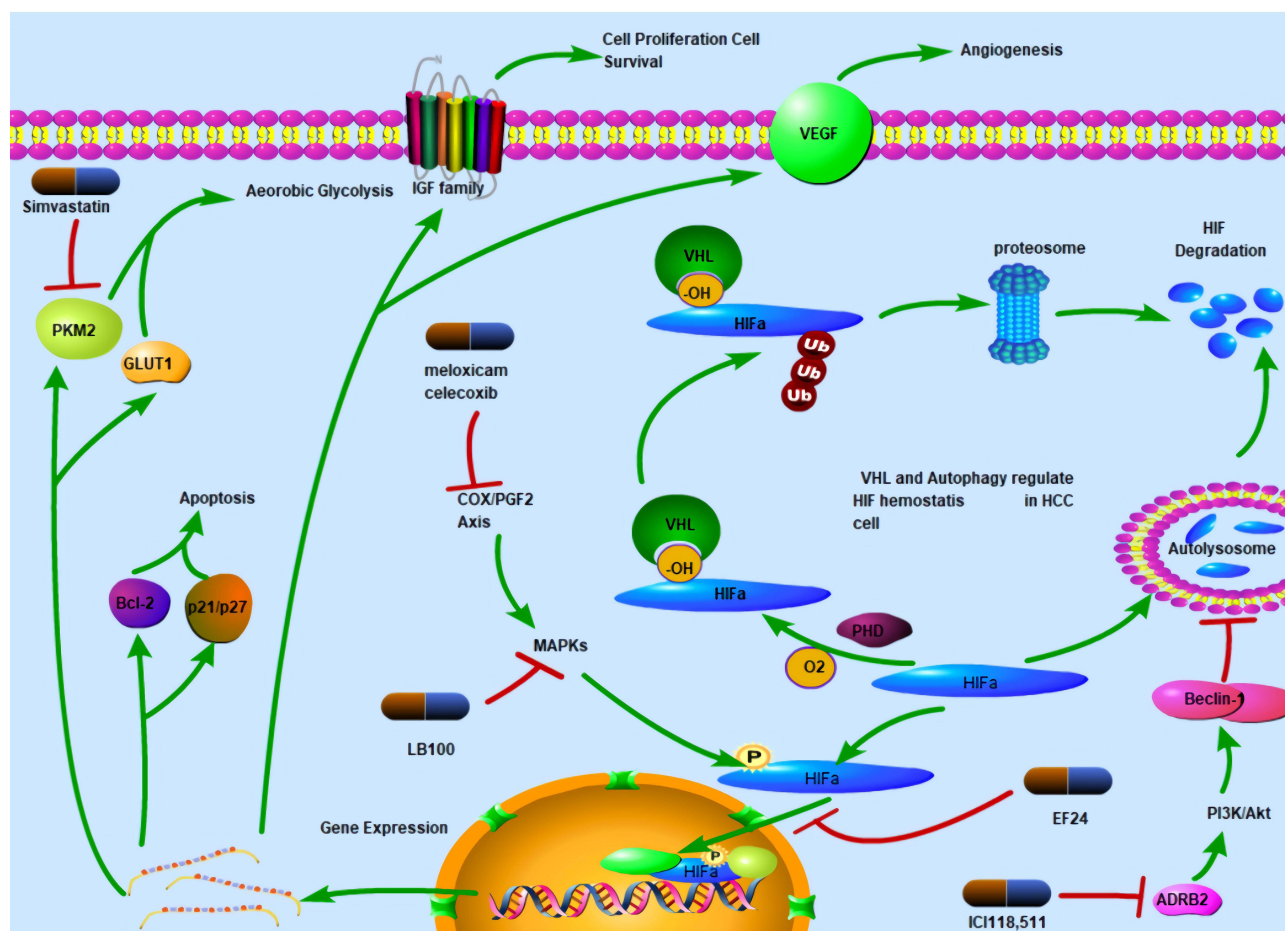
**Keywords:** hepatocellular carcinoma, sorafenib, drug resistance, combination therapy, target therapy

## Introduction

Hepatocellular carcinoma (HCC) is insidious in nature and has a low early diagnosis rate. Surgical resection, local ablation, and liver transplantation are potential curative treatment options for early-stage HCC. Sorafenib has long been the main targeted drug used for the systemic treatment of advanced liver cancer. It is an oral multi-kinase inhibitor and inhibits intracellular serine/threonine kinases (including Raf-1, wild-type B-Raf, and mutant B-Raf) and receptor tyrosine kinases (RTKs) (including the vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptors  $\beta$  and c-KIT, FMS-like tyrosine kinase 3, and RET), thereby inhibiting tumor proliferation and angiogenesis.<sup>1,2</sup> However, only 35–43% of patients respond to sorafenib, and most of them relapse within 6 months.<sup>3,4</sup> Therefore, elucidating the mechanisms underlying sorafenib resistance (SR) is important for the improvement of survival in HCC patients. Because of the existence of complicated signaling cross-talk within HCC cells, which leads to the development of multiple compensatory mechanisms and alternative pathways, HCC patients respond differentially to sorafenib. Elucidating the mechanisms underlying SR and enhancing drug sensitivity are key strategies for improving the clinical efficacy of sorafenib.

## Alleviation of SR Through the Hypoxia-Related Pathway in HCC Cells Mechanism of Hypoxia-Related SR

Hypoxia is commonly occurs in solid tumors such as HCC.<sup>5</sup> Since the speed of vasculogenesis is not sufficient to meet up with rapid tumor growth, oxygen and nutrient supply is usually limited. Hypoxia inducible factors (HIFs) are the main transcriptional regulators of the adaptive response to hypoxia in HCC cells.<sup>6</sup> Oxygen content is a critical determinant of cellular HIF homeostasis. HIFs contain an oxygen-dependent degradation domain (ODDD) of approximately 200 residues that regulates their degradation. The ODDD contains two oxygen-dependent prolyl hydroxylation sites, both of which can be hydroxylated by prolyl hydroxylases.<sup>7</sup> Under normal oxygen supply conditions (normoxia), hydroxylated HIF1 $\alpha$  is recruited by the von Hippel-Lindau ubiquitination complex (VHL) and degraded in a ubiquitination-dependent manner (Figure 1). In addition,



**Figure 1** Mechanism of HIF-dependent sorafenib sensitization. HIF $\alpha$  is hydroxylated by prolyl hydroxylases under normoxia conditions and binds with VHL. Following ubiquitination by VHL, HIF $\alpha$  is degraded by 26S proteasomes. HIF $\alpha$  can be packaged by autophagosomes and transported to lysosomes for hydrolysis. ICI118,511 can inhibit autophagy-dependent HIF degradation by inhibiting ADRB2. HIF $\alpha$  can be translocated to the nucleus where it functions as a transcription factor. This process is pharmacologically inhibited by EF24. HIF translocation is also dependent on MAPKs located in the cytosol. LB100 inhibits HIF function through MAPK inhibition. Meloxicam and celecoxib can also inhibit MAPK through the COX-PGF2 axis, thereby inhibiting HIF translocation and function. HIFs transcriptionally activate multiple genes, including Bcl-2 and p21/p27, which mediate cell apoptosis, PKM2 and GLUT1, induce metabolic reprogramming and shift cell energy metabolism to aerobic glycolysis. Simvastatin inhibits PKM2 and sensitizes HCC cells to sorafenib. HIFs also regulate cell proliferation and angiogenesis by upregulating IGF and VEGF levels.

HIF1 $\alpha$  can be degraded through the autophagy pathway.<sup>8</sup> Under hypoxia-induced stress conditions, HIF cannot be hydroxylated or stabilized for the activation of the transcription of over 40 genes that facilitate angiogenesis and the shift in cell energy metabolism to anaerobic glycolysis.<sup>9</sup> HIF1 $\alpha$  has been identified to be relevant in chemoresistance, tumor aggressiveness, and poor prognosis in HCC patients.<sup>10</sup> Interestingly, HIFs tend to exhibit dual characteristics under sorafenib-induced stress conditions. As a drug with anti-angiogenesis activity, sorafenib has VEGF as one of its main targets.<sup>11</sup> In vivo studies have shown that sorafenib downregulates the synthesis of both HIF1 $\alpha$  and VEGF.<sup>12</sup> Of note, VEGF is also a key downstream factor that affects HIF expression. However, long-term treatment with sorafenib paradoxically induces an increase in HIF transcription and translation.<sup>13</sup> This could be because the hypoxia microenvironment, which develops due to the anti-angiogenesis effects of sorafenib, selects for more resistant and invasive HCC clones.<sup>13,14</sup>

## HIF1 $\alpha$

As HIF1 $\alpha$  contributes to SR in HCC cells, its inhibition could be a potential strategy for overcoming SR (Figure 1). Liang et al found that EF24 suppresses HIF translocation to the nucleus and upregulates VHL expression, thereby inducing an increase in HIF1 $\alpha$  degradation through proteasome activity.<sup>13</sup> This enhances the antitumor effects of sorafenib. In addition, curcumin, which has a similar structure to EF24, was found to potentiate the effects of sorafenib.<sup>15</sup> Wu et al found that ICI118,511, an ADRB2 antagonist, in combination with sorafenib, destabilized HIF1 $\alpha$ , thereby inhibiting

tumor growth.<sup>16</sup> Mechanistically, ADRB2 signaling inhibits autophagy by facilitating Beclin1 homodimer formation in an Akt-dependent manner. Inhibition of autophagy further stabilizes HIF1 $\alpha$ , thereby inducing SR.<sup>16</sup> Thus, the pharmacological inhibition of ADRB2 promotes autophagy and HIF1 $\alpha$  degradation. Of note, ADRB2 is also degraded in a VHL-dependent manner.<sup>17</sup> Since VHL is the main regulatory factor for HIF, it is hypothesized that targeting the HIF/VHL axis might serve as a potential therapeutic strategy for reversing SR. However, the role of VHL in HCC chemoresistance still needs to be further investigated. Liu et al found VHL instability to enhance HCC metastasis and adaption to the hypoxia microenvironment.<sup>18</sup> Furthermore, Feng et al found sorafenib-resistant HCC cells to be more sensitive to simvastatin than non-resistant cells in LM3 cells.<sup>19</sup> Mechanistically, HCC cells evade the effects of sorafenib by upregulating the expression levels of both PKM2 and HIF1 $\alpha$  and by shifting energy metabolism from OXPHOS to aerobic glycolysis. Simvastatin inhibits PKM2 and HIF1 $\alpha$ , thereby reversing SR.<sup>19</sup>

## HIF2 $\alpha$

The HIF family is constituted of three members (HIF1 $\alpha$ , HIF2 $\alpha$ , and HIF3 $\alpha$ ). HIF2 $\alpha$  is closely related to HIF1 $\alpha$  homologues.<sup>20</sup> HIF1 $\alpha$  and HIF2 $\alpha$  jointly control hypoxia response in HCC cells.<sup>21</sup> Clinical data have shown that the overexpression levels of both HIF1 $\alpha$  and HIF2 $\alpha$  are reliable poor prognostic markers for HCC.<sup>22</sup> Interestingly, sorafenib was found to exert downregulatory bioeffects against HIF1 $\alpha$  expression, and to shift hypoxic response from an HIF1 $\alpha$ -dependent pathway to an HIF2 $\alpha$ -dependent pathway.<sup>23</sup> This consequently leads to the upregulation of VEGF and cyclin D1 expression, and SR. Thus, treatment strategies targeting HIF1 $\alpha$  alone may not be sufficient to overcome SR; HIF2 $\alpha$  targeting may equally be necessary for sensitizing HCC cells to sorafenib (Figure 1). Dong et al found that the activation of COX-2/PGE2 axis effectively induced a decrease in VHL levels and stabilized HIF2 $\alpha$ . In addition, it was found to enhance HIF2 $\alpha$  activity by promoting HIF2 $\alpha$  nuclear translocation via the p38 mitogen-activated protein kinase (MAPK) pathway. Consequently, VEGF, cyclin D, and TGF $\alpha$ /EGFR were all activated, and this led to SR. The COX-2 inhibitors, meloxicam and celecoxib, were found to enhance response to sorafenib both in an in vivo CDX model and in vitro.<sup>24</sup> Furthermore, hypoxic conditions were shown to activate the MAPK signaling pathway, consequently leading to SR through the enhancement of p-Smad3-dependent B-cell lymphoma (Bcl)-2 inhibition. Interestingly, LB-100, a serine/threonine protein phosphatase 2A inhibitor, which was found to be functional only in hypoxic environments, was shown to sensitize cells to sorafenib. LB-100 sensitizes cells to sorafenib by upregulating p-Smad3 expression, thereby decreasing Bcl-2 expression and increasing HCC cell apoptosis.<sup>25</sup> Furthermore, Ma et al found that the antitumor drug, 2-methoxyestradiol, which acts by dysregulating HIF-1 $\alpha$  expression, showed synergistic effects with sorafenib by inhibiting both the expression and translocation of HIF-1 $\alpha$  and HIF-2 $\alpha$ .<sup>23</sup> As HIF-2 $\alpha$  is upregulated in HCC cells and contributes to chemoresistance, its downregulation using the antidiabetic drug, metformin, was also found to sensitize HCC cells to sorafenib both in vitro and in vivo.<sup>26,27</sup> Moreover, regorafenib was found exhibit synergistic effects with metformin in HCC cells through a similar mechanism.<sup>28</sup>

## Hypoxia and the Nuclear Factor $\kappa$ -Light-Chain-Enhancer of Activated B Cells (NF- $\kappa$ B) Pathway

The NF- $\kappa$ B pathway, which is a critical downstream pathway for HIF regulation, plays a critical role in HCC cell resistance to sorafenib.<sup>29</sup> Studies have shown that NF- $\kappa$ B is significantly activated in sorafenib-resistant HCC cells.<sup>29</sup> Cheng et al demonstrated that the inhibition of interleukin-1 receptor-associated kinase 1 (IRAK1) axis, which is an upstream regulator of the NF- $\kappa$ B pathway, using a specific IRAK1/4 kinase inhibitor, induces effects that are synergistic to those of sorafenib.<sup>30</sup> In line with these findings, Alsaied et al found that triptolide, which decreases NF- $\kappa$ B activity, in combination with sorafenib, can significantly control mouse tumor growth. Of note, in this study, 10 mg/kg of sorafenib, which is lower than 10% of the dose currently prescribed for HCC patients, was found to exert significant effects in combination with triptolide in an in vivo HCC model.<sup>31</sup> CD47 is a downstream NF- $\kappa$ B regulatory factor; its inhibition using anti-CD47 antibodies was found to induce an increase in cell sensitization to sorafenib.<sup>29</sup> Furthermore, as an antiangiogenic drug, sorafenib was shown to decrease vessel density and induce the development of a hypoxic microenvironment for tumor cell destruction.<sup>32</sup> Vorinostat, a traditional and well-discussed HDACi was shown to exhibit

synergistic effects with sorafenib and to induce apoptosis and cell cycle stagnation in HCC cells.<sup>33</sup> Mechanistically, vorinostat promotes NF- $\kappa$ B activation and induces cancer cell progression and chemoresistance (Figure 1). However, sorafenib inhibits NF- $\kappa$ B and its downstream signaling pathway, thereby further inhibiting vorinostat-induced HCC progression and drug resistance.<sup>34</sup> It has been shown that the strategy of using sorafenib and HDACi in combination has yielded unsatisfactory results in patients with HCC expressing low CD95.<sup>35</sup> Hence, Hamed et al found that TRAIL, a death receptor agonist, in combination with sorafenib and HDACi induced apoptosis more significantly than TRAIL or [sorafenib + HDACi] in CD95 null Huh7 HCC cells.<sup>35</sup> A Phase I/II study on the sorafenib, HDACi, and resminostat combination is ongoing.<sup>36</sup> This triple combination therapy offers a novel potential strategy for the reduction of SR in HCC cells (Figure 1).

## Trans-Arterial Chemoembolization (TACE) in Combination with Sorafenib

TACE is recognized as the most common nonsurgical treatment method for HCC.<sup>37</sup> Trans-arterial chemoembolization involves the infusion of cytotoxic agents mixed with lipiodol into hepatic arteries.<sup>38</sup> This induces cell apoptosis, and subsequently, cancer tissue necrosis as a result of local angiogenesis inhibition in HCC, which is a well-vascularized tumor type. Consequently, several growth factors, including HIF-1 $\alpha$  and VEGF, are activated. Several studies have reported the efficacy of the TACE plus sorafenib strategy. A randomized, multi-center, prospective clinical trial (NCT01217034) compared the efficacy and safety of TACE plus sorafenib with those of TACE alone in patients with unresectable HCC. Median progression free survival (PFS) significantly increased in patients treated with the combination therapy than in those treated with TACE alone (25.2 vs 13.5 months;  $p=0.006$ ).<sup>39</sup> Furthermore, a meta-analysis carried out by Zhang et al also confirmed the clinical efficacy of the combination therapy to be better than that of TACE alone.<sup>40</sup> Li et al confirmed that serum VEGF concentrations were significantly elevated following TACE in rabbit model.<sup>41</sup> This suggests that VEGF is a key factor that enables HCC cells to survive TACE treatment. As a VEGF antagonist, sorafenib specifically inhibits cell clones that survive TACE. However, the biological mechanism underlying the action of TACE plus sorafenib, as well as the reason why the combination therapy shows better clinical efficacy than TACE alone, still need to be determined.

## Energy Metabolism

### Glutamine Metabolism

Metabolic reprogramming contributes significantly to tumor metastasis and drug resistance.<sup>42</sup> Recently, it was discovered that cancer cells reprogram nutrient metabolism in the tumor microenvironment.<sup>43</sup> Cancer cells shift their energy metabolism to glutamine and lipids but not to glucose as initially believed. In line with this, Kim et al observed glutamine metabolism and reductive glutamine carboxylation in sorafenib-resistant HCC cells.<sup>44</sup> Based on this, targeting glutamine metabolism could be a potential strategy for reversing SR. The glutaminase inhibitor, bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide, also known as BPTES, was found to be effective in sensitizing HCC cells to sorafenib. Besides, oxoglutarate dehydrogenase-like (OGDHL), one of rate-limiting components of the mitochondrial multi-enzyme OGDH complex and plays a critical role in down-regulating reductive glutamine metabolism.<sup>45</sup> Dai et al found that lower expression of OGDHL was associated with advanced tumor stage, significantly worse survival and more frequent tumor recurrence in 681 patients.<sup>45</sup> Over expression of OGDHL enhanced sorafenib chemo-sensitization to HCC CDX models.<sup>45</sup> Kim et al attribute this glutamine-dependent energetic shift to peroxisome proliferator-activated receptor- $\delta$  (PPAR $\delta$ ), as its inhibition by GSK0660 was found to effectively reverse SR.<sup>44</sup>

### Lipid Metabolism

Lally et al highlighted the importance of de novo lipogenesis (DNL) in HCC energy metabolism. Acetyl-CoA carboxylases (ACC) 1 and 2 are both rate-limiting enzymes in the DNL process, which is activated by AMPK. ND-654, a liver-specific ACC inhibitor, was found to improve survival in HCC-bearing rats in combination with sorafenib through the inhibition of hepatic DNL.<sup>46</sup>



## ROS

Increasing evidence shows that sorafenib enhances oxidative stress in HCC cells.<sup>47,48</sup> However, HCC cells upregulate the expression of antioxidant genes through different mechanisms to avoid sorafenib-induced oxidative damage. For instance, the facilitates chromatin transcription (FACT) complex, a histone chaperone,<sup>49</sup> was found to be upregulated in HCC cells. The FACT complex is a key regulatory factor for NRF2 expression and its downstream factors include NQO1, TXNRD1, and TKT, which are essential for HCC evasion of oxidative damage.<sup>49,50</sup> Thus, by inhibiting the FACT complex and inducing oxidative stress, curaxin showed promising synergistic effects with sorafenib *in vivo* and *in vitro*.<sup>50</sup> In addition, auranofin (AUR)-induced inhibition of TXNRD1 transcription, which is mediated by NRF2 and down-regulated in HCC cells,<sup>51</sup> also induces an increase in ROS levels and leads to sorafenib sensitization in these cells.<sup>52</sup> Targeting the FACT/NRF2/TXNRD1 axis and inducing ROS production could be a promising strategy for sensitizing HCC cells to sorafenib. The curaxin and sorafenib combination also exhibits acceptable safety profiles in mice. However, these studies are mostly experimental and there is need for further clinical trials to be carried out to validate the safety and effectiveness of these agents.

## Signaling Pathways

### Upstream RTKs

Transforming growth factor  $\beta$  (TGF $\beta$ ) is a key upstream RTK regulatory factor. TGF $\beta$  was found to be upregulated in HCC patients,<sup>53</sup> and over-activated especially in sorafenib-resistant HCC patients.<sup>54</sup> Matsuda et al found that TGF enhanced SR in HCC.<sup>6</sup> Valproic acid (VPA) is a histone deacetylase inhibitor that is used as an anti-epileptic agent. Interestingly, VPA was found to be effective in reversing TGF $\beta$ -induced SR and exhibited synergistic effects with sorafenib in HCC cells.<sup>55,56</sup> Mechanistically, VPA modulates the Jagged 2-mediated Notch1 signaling pathway and reverses the EMT phenotype, which are significantly correlated with chemoresistance, especially resistance to sorafenib, in HCC cells.<sup>55</sup> The TGF $\beta$ RI kinase inhibitor, LY2157399, was found to effectively enhance sorafenib-induced apoptosis in HCC cells.<sup>57</sup> Studies have shown that TGF $\beta$  can upregulate receptor tyrosine kinase (RTK) levels. Furthermore, RTKs, including IGF1R and EGFR, have been shown to be responsible for chemoresistance to sorafenib.<sup>58,59</sup> Thus, LY2157399 can improve sensitivity to sorafenib by suppressing RTK-induced SR via the inhibition of TGF $\beta$ . In consonance with these findings, the liver X receptor (LXR) agonist, T0901317, was also found to be effective in inhibiting RTK function and sensitizing HCC cells to sorafenib. LXR is a key factor involved in liver lipid metabolism<sup>60</sup> and its activation induces cholesterol efflux and interferes with the stability of the cytomembrane, thereby suppressing the sorafenib-dependent recruitment of multiple RTKs, including MET and EGFR, in lipid rafts; this leads to an enhancement of the antitumor effects of sorafenib.<sup>61</sup>

### Downstream RTKs

Sorafenib is a well-known tyrosine kinase inhibitor, and it inhibits several different targets.<sup>62</sup> However, compensatory pathways are usually activated in HCC cells to evade the cytotoxic effects of sorafenib. Thus, targeting compensatory signaling pathways is a potential strategy for alleviating chemoresistance to sorafenib.

Increasing evidence has shown that drug resistance can be acquired by HCC cells through RTK-mediated activation of several signaling pathways. SRC homology 2 domain-containing phosphatase 2 (SHP2) is an important downstream RTK regulatory factor. It has been shown that SHP2 is activated by sorafenib in HCC cells and that further activation of SHP2 induces the suppression of STAT3, an important transcription factor that has been shown to be involved in chemoresistance in different cancer types, including HCC.<sup>63–67</sup> Sorafenib has been shown to suppress STAT3 function through SHP2 activation,<sup>68,69</sup> thereby further inducing apoptosis in HCC cells. In addition, by directly activating SHP-1, dovitinib, another multiple kinase inhibitor, inhibits STAT3 and exhibits synergistic effects with sorafenib.<sup>70</sup> Moreover, SC-2001, which has a similar structure to obatoclax, has been shown to exhibit synergistic effects with sorafenib by inducing RFX-1/SHP-1 expression, and consequently, STAT3 suppression.<sup>71</sup> Furthermore, Leung et al found that SHP2 inhibition using SHP099 also sensitizes HCC cells to sorafenib. It has been reported that RTKs can induce the activation of the MEK/ERK and Akt signaling pathways, thereby inducing SR.<sup>72</sup> In summary, SHP2 could be an important

downstream effector of RTKs, which are key inducers of SR, and induces sorafenib sensitization through dephosphorylation and STAT3 inhibition. The dual nature of the interaction between SHP and sorafenib still needs to be further investigated.

## The Akt and c-Met Pathways

The Akt pathway is an important compensatory pathway in HCC cells under sorafenib-induced stress.<sup>73</sup> Several Akt inhibitors are under investigation in clinical trials to determine their efficacy in HCC treatment.<sup>73</sup> Increasing evidence has shown that the IGF/FGF axis, which is an upstream Akt regulator, plays an important role in acquired SR.<sup>74</sup> The inhibition of these pathways may contribute to the restoration of HCC cell sensitivity to sorafenib and further increase this sensitivity.<sup>74</sup> For example, Wang et al found that ceritinib, which is an IGFR inhibitor initially used for the treatment of non-small cell lung cancer, could sensitize HCC cells to sorafenib by inhibiting the IGF1R/Akt pathway both in vitro and in xenograft and HCC mouse models.<sup>75</sup> Interestingly, despite the significant IGF1R inhibition induced by shRNA and ceritinib, they do not exhibit significant suppressive effects against HCC cells when used alone. Ceritinib exhibits significant inhibitory effects against HCC cell proliferation when used in combination with sorafenib as compared to when it is used alone. In addition, the IGFR inhibitor, linsitinib, and the FGFR inhibitor, brigatinib, were found to be effective in decreasing sorafenib-resistant HCC cell viability through the Akt pathway.<sup>74</sup> In line with this, Xu et al found that liver-specific microRNA-122, which targets IGF1R and inhibits its expression, was significantly downregulated in sorafenib-resistant cells. The IGF-1R inhibitors, PPP and NVP-AEW541, in combination with sorafenib, significantly induced cell apoptosis and decreased drug tolerance in vitro.<sup>58</sup> In addition, Zhai et al found that bufalin, a natural compound extracted from bufonid, reverses acquired SR by downregulating Akt phosphorylation. Moreover, Lu et al found that 20(S)-Ginsenoside Rg3 sensitizes HCC cells to sorafenib through the PI3K/Akt pathway. The PI3K inhibitor, SF1126, was also found to be effective in reversing SR in vivo.<sup>76</sup>

However, targeting the Akt pathway may not be sufficient to reverse sorafenib chemoresistance due to the activation of the c-Met pathway, which can function as a compensatory pathway to enhance HCC cell progression and proliferation.<sup>73</sup> Thus, Han et al developed a dual inhibition therapeutic strategy that combined the Akt inhibitor, MK2206, and the c-Met inhibitor, capmatinib, with sorafenib, and this combination showed significant effectiveness in inducing apoptosis and cell cycle arrest. These studies provide new evidence to support further clinical trials.

## Natural Compounds and Nano-Particles

Several natural compounds have been found to show synergistic effects with sorafenib. A study compared the sensitization effect of different natural phenolic compounds, including curcumin (Cur), quercetin (Que), and kaempferol (Kmf), with that of sorafenib. Cur and Kmf were found to be effective in sensitizing both Hep3b and HepG2 cells to sorafenib by decreasing cyclins A, B2, and D1 levels, and this led to S-phase and G2/M-phase cell arrest. Furthermore, concomitant treatment with sorafenib and Cur also induced an increase in apoptosis by decreasing Bcl extra-large protein levels and increasing Bcl-2-associated X protein, caspase-3, and caspase-9 levels.<sup>15</sup> In this study, Que was found to be ineffective in sensitizing cells to sorafenib. However, in another study,<sup>77</sup> it was found to be effective in sensitizing cells to sorafenib when packaged into dual-targeted lactobionic acid (LA)/ lactoferrin (LF)-NCs. These nanocapsules, which were modified by LF and LA/glycyrrhetinic acid (GA), exhibited increased selectivity and specificity due to the presence of asialoglycoprotein and GA receptors on liver cancer cells and LF receptor overexpression.

## Conclusion

HCC has the second lowest cancer survival rate (20%) worldwide.<sup>78</sup> Over the last decade, sorafenib has been the only first-line agent available for the treatment of advanced liver cancer. In this study, we review key factors involved in SR, including hypoxia, metabolic factors, and the corresponding signaling pathways. Through the elaboration of the mechanisms involving these resistance factors, we listed their related pharmacological treatments, which have shown potential in alleviating SR. Recently, Lenvatinib was approved as a first-line agent for the treatment of HCC, and showed almost the same efficiency as sorafenib. However, the occurrence of resistance to lenvatinib has also become a major obstacle to its use in improving prognosis in HCC patients.<sup>79</sup> For a long time, HCC has been known to be insensitive to chemotherapy, including

TKIs treatment.<sup>80</sup> There is an urgent need to understand the mechanisms underlying this resistance to potentiate the antitumor effects of sorafenib and identify novel chemotherapeutic agents. Therefore, through the description of the mechanisms underlying SR and the summarizing of corresponding SR inhibitors, this review attempts to provide potential solutions to this challenge and provide a significant reference for treating TKI resistance. Given the high degree of heterogeneity and the complexity of SR in HCC, in the future, we will focus on the exploration of the molecular, genetic, and cellular mechanisms underlying drug resistance in HCC cells. Some new tools, including CRISPR/Cas9 technology, 3-dimensional culturing, spheroids, and organoids can be used to identify specific molecular targets and investigate the tumor microenvironment during HCC chemoresistance. In vivo models such as patients, cell-line derived xenografts, and transgenic animals are still relevant for the confirmation of the synergistic effects of different drugs with sorafenib.

## Abbreviations

HCC, hepatocellular carcinoma; LF, lactoferrin; RTK, receptor tyrosine kinase; SR, sorafenib resistance; HIF, hypoxia inducible factor; ODDD, oxygen-dependent degradation domain; VHL, von Hippel-Lindau ubiquitination complex; MAPK, mitogen-activated protein kinase; SHP2, SRC homology 2 domain-containing phosphatase 2; GA, glycyrrhetic acid; Bcl, B-cell lymphoma; LXR, liver X receptor; IRAK, interleukin-1 receptor-associated kinase; TACE, trans-arterial chemoembolization.

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## Disclosure

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