

## Downregulation of signal transducer and activator of transcription 3 by sorafenib: A novel mechanism for hepatocellular carcinoma therapy

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### Abstract

Hepatocellular carcinoma is one of the most common cancers worldwide, and a leading cause of cancer-related death. Owing to unsatisfactory clinical outcomes under the current standard of care, there is a need to search for and identify novel and potent therapeutic targets to improve patient outcomes. Sorafenib is the first and only approved targeted therapy for the treatment of hepatocellular carcinoma. Besides functioning as a multiple tyrosine kinase, sorafenib also acts via a kinase-independent mechanism to target signal transducer and activator of transcription 3 (STAT3) signaling in hepatocellular carcinoma cells. STAT3 is a key regulator of inflammation, cell survival, and tumorigenesis

of liver cells, and the high percentage of hepatocellular carcinoma cells with constitutively active STAT3 justifies targeting it for the development of novel therapeutics. Sorafenib inactivates STAT3 and STAT3-related signaling by inducing a conformational change in and releasing the autoinhibition of Src homology region 2 domain-containing phosphatase-1. This phosphatase negatively regulates STAT3 activity, which leads to the subsequent apoptosis of cancer cells. The novel anti-cancer property of sorafenib will be discussed in this review, not only adding information regarding its mechanism of action but also providing an innovative approach for the development of cancer therapeutics in the future.

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**Key words:** Hepatocellular carcinoma; Sorafenib; Signal transducer and activator of transcription 3; Target therapy; Kinase-independent

**Core tip:** Hepatocellular carcinoma (HCC) is one of the major cancers worldwide, for which the only approved target therapy is sorafenib. In addition to its previously characterized kinase inhibition, sorafenib also acts *via* a kinase-independent mechanism to target signal transducer and activator of transcription 3 (STAT3) signaling in HCC cells. This review discusses these findings, adding to the knowledge concerning the mechanisms of action of sorafenib as well as exploring the potential use of STAT3 as a therapeutic target in future cancer drug development.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading primary malignancy of the liver, the fifth most common cancer and the third leading cause of cancer-related deaths worldwide<sup>[1,2]</sup>. A survey conducted by the World Health Organization found more than 700000 newly diagnosed cases of HCC in 2008, which corresponds to an age-adjusted incidence of 16 cases per 100000 inhabitants worldwide and up to 35.5 cases per 100000 male inhabitants of eastern Asia<sup>[3]</sup>.

Treatment choices for HCC patients are made based on residual liver function and, as with other cancers, on the stage of disease as well as the patient's general condition and comorbidities. For patients with early stage disease, percutaneous ablation, surgical resection, and liver transplantation offer the highest rates of complete response and, thus, the highest potentials for cure<sup>[4]</sup>. Unfortunately, because of a lack of associated signs and symptoms at the early stage, the majority of HCC patients are diagnosed with advanced disease and only 20%-30% are eligible for curative surgical resection<sup>[1]</sup>. Furthermore, nearly 90% of HCC develops in the background of chronic liver diseases that are either caused by chronic inflammation related to various etiologies, including hepatitis B or C infection and alcohol intake, or other hepatic toxin exposure, and even non-alcoholic fatty disease<sup>[2,5]</sup>. The complexity and heterogeneity of HCC tumorigenesis contributes to an intrinsic resistance of tumor cells to conventional chemotherapy and radiotherapy. Until recently, there were no effective treatments available for patients diagnosed with advanced stage HCC or whose disease deteriorated to an advanced stage after other treatments failed.

Although the first drug that demonstrated improvement in overall survival of patients with advanced HCC was sorafenib, an inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity<sup>[6,7]</sup>, clinical trials testing several additional potent VEGFR inhibitors, such as sunitinib and brivanib, failed to show positive results<sup>[1,8,9]</sup>. The failures of these trials are thought to be multifactorial, including a lack of full understanding of the critical drivers of tumor progression<sup>[10]</sup>. In light of these results, it is essential to revisit the therapeutic mechanisms of sorafenib, focusing on the VEGFR-independent effects. This review outlines an important VEGFR-independent mechanism by which sorafenib induces apoptosis of HCC cells, via inhibition of signal transducer and activator 3 (STAT3) and its signaling pathway by increasing Src homology region 2 domain-containing phosphatase 1 (SHP-1) activity. This novel mechanism provides a promising foundation for further development of potent anti-cancer therapeutics.

## STAT FAMILY PROTEINS

The highly conserved STAT family proteins were first identified in 1994 as acute phase response factors associated with interleukin-6 (IL-6) stimulation<sup>[11]</sup>. STAT pro-

teins, including STAT1-4, STAT5a, 5b and STAT6<sup>[12,13]</sup>, are inactive and primarily located in the cytoplasm of non-stimulated cells. However, certain stimuli cause the activation and dimerization of STAT proteins by phosphorylation of specific tyrosine residues. The dimerized STATs are then translocated to the nucleus and enhance the transcription of genes<sup>[12]</sup> that govern various important cellular functions, such as cell differentiation, survival and immune response<sup>[14]</sup>. Among all the STAT proteins, STAT3 is particularly associated with oncogenesis<sup>[15,16]</sup>.

### Regulation of STAT3 activity

STAT3 is activated by cytokines, growth factors, carcinogens, stress, infection and radiation<sup>[14,17,18]</sup>, which cause phosphorylation of tyrosine 705. Various receptors that have tyrosine kinase activity can phosphorylate this residue, such as epidermal growth factor receptor, VEGFR and platelet-derived growth factor receptor (PDGFR), as well as other non-receptor tyrosine kinases, including Janus kinases (JAKs) and IL-6 receptors<sup>[19,21]</sup>. Additionally, the activity of STAT3 is also affected by phosphorylation of the serine residue at position 727 and acetylation of a lysine residue at position 685<sup>[22,23]</sup>.

As tyrosine phosphorylation plays a major role in its activation, it is not surprising that tyrosine phosphatases negatively regulate STAT3. The protein tyrosine phosphatase superfamily, comprised of more than 100 members in humans, is classified into three subgroups: the classical protein tyrosine phosphatases (PTPs), dual-specificity phosphatases, and low molecular weight phosphatases<sup>[24]</sup>. PTPs are further divided into transmembrane tyrosine phosphatase CD45 and the non-transmembrane PTPs, including SHP-1, SHP-2, PTP-1B and T-cell protein tyrosine phosphatase. PTPs function is closely associated with JAKs, as the absence of SHP-1 predisposes cancer cells to constitutive activation of the JAK3/STAT3 pathway and tumorigenesis of anaplastic lymphoma kinase (ALK)+ large cell lymphoma<sup>[25]</sup>. Additionally, protein inhibitors of activated STAT (PIAS) and suppressors of cytokine signaling (SOCS) proteins are important negative regulators of STAT3-associated signals, and abnormal expression of these two protein families has been linked with many inflammatory diseases and cancers<sup>[14,26,27]</sup>.

### STAT3 in HCC tumorigenesis

Constitutive STAT3 activity is observed in various cancer cell lines and tumor tissues, including breast, liver, lung, pancreas and prostate cancers, and melanoma<sup>[15,16,28]</sup>. He *et al.*<sup>[29]</sup> found that nearly 60% of clinical HCC tumor samples showed nuclear phosphorylated-STAT3 staining, which correlated with the HCC aggressiveness. These observations suggest that STAT3 signaling is turned on in human HCC.

Hepatocarcinogenesis is a long and complex process involving chronic inflammation, oxidative stress, stimulation of cytokines (such as IL-6) and growth factors, loss of phosphatase function, or epigenetic modifications that silence SOCS proteins; these various changes can activate STAT3. Once activated, STAT3 may induce a

series of signals that promote HCC proliferation (such as cyclin D1 and survivin), angiogenesis, and survival (such as Bcl-2 and Bcl-XL), and help tumors evade host immune surveillance<sup>[30-33]</sup>. Whereas activation of STAT3 by hepatitis C virus core protein or hepatitis B virus x protein promotes HCC growth<sup>[34,35]</sup>, the downregulation of STAT3 reduces the growth of HCC *in vitro* and *in vivo*<sup>[36,37]</sup>. Furthermore, HCC development induced by diethylnitrosamine (DEN) in mice was prohibited when STAT3 signaling was reduced or conditionally knocked out<sup>[29,38,39]</sup>. Moreover, DEN-induced HCC was promoted and the expression of STAT3 was enhanced when negative regulators of STAT3 were deleted or IL-22 was overexpressed<sup>[40-42]</sup>. Collectively, these data demonstrate the role of STAT3 in promoting HCC tumorigenesis and indicate that it is a highly attractive target for treatment.

## SORAFENIB IN HCC

### **The clinical efficacy of sorafenib**

The efficacy of sorafenib (Nexavar) for the treatment of advanced HCC has been confirmed by two large, prospective, randomized, double-blind clinical trials<sup>[6,7]</sup>. First, in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study that enrolled 602 patients with advanced HCC from Europe, North America, South America and Australia, a significant improvement in overall survival was observed for patients who received 400 mg sorafenib twice daily (10.7 mo *vs* 7.9 mo with placebo)<sup>[6]</sup>. Later in the Asia-Pacific trial, Cheng *et al*<sup>[7]</sup> validated the anti-cancer effects of sorafenib in 271 patients from the Asia-Pacific region, with significant improvements in overall survival and time-to-progression.

The safety profile of sorafenib was established by the results of the two previously mentioned studies and in the large-scale non-interventional phase IV Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment With Sorafenib (GIDEON) study<sup>[43]</sup>, which followed 3202 sorafenib-treated unresectable HCC patients with Child-Pugh grade A and B liver functions. Although more than 80% of patients experience adverse events, only 9.3% of patients in the GIDEON study had grade 3-4 drug-related adverse events. The most frequent adverse events were diarrhea, fatigue and hand-foot skin reactions. Together, these data have established sorafenib as the standard of care for advanced HCC.

### **Therapeutic mechanism of sorafenib: more than a kinase inhibitor**

Sorafenib was originally developed to disrupt the Ras-Raf-MEK1/2-ERK1/2 signaling pathway by specifically targeting Raf-1 kinase<sup>[44]</sup>. Wilhelm *et al*<sup>[44]</sup> were the first to show that sorafenib inhibited the *in vitro* proliferation and transformation of pancreatic and colon cancer cell lines, and suppressed *in vivo* xenografted tumor growth. Furthermore, they demonstrated that the anti-cancer ef-

fects correlated with the inhibition of MEK and ERK phosphorylation. Several other investigators later found that sorafenib also affects other receptor tyrosine kinases, including VEGFR-2,3, PDGFR- $\beta$ , Fms-like tyrosine kinase-3, and fibroblast growth factor receptor-1<sup>[45-47]</sup>.

Our group was the first to report that STAT3 plays an important role in mediating the effects of sorafenib on tumor necrosis factor-related apoptosis-induced ligand (TRAIL)-sensitization<sup>[48]</sup>. Treatment of HCC cells with sorafenib and recombinant TRAIL (LBY 135) resulted in the downregulation of STAT3 and STAT3-related anti-apoptotic signaling (Mcl-1, cyclin D1, and survivin) and apoptosis of HCC cells. Furthermore, we generated a series of sorafenib derivatives devoid of kinase inhibition and found that they also inhibited STAT3 expression by increasing the activity of its negative regulator, SHP-1<sup>[49,50]</sup>.

### **Sorafenib and SHP-1**

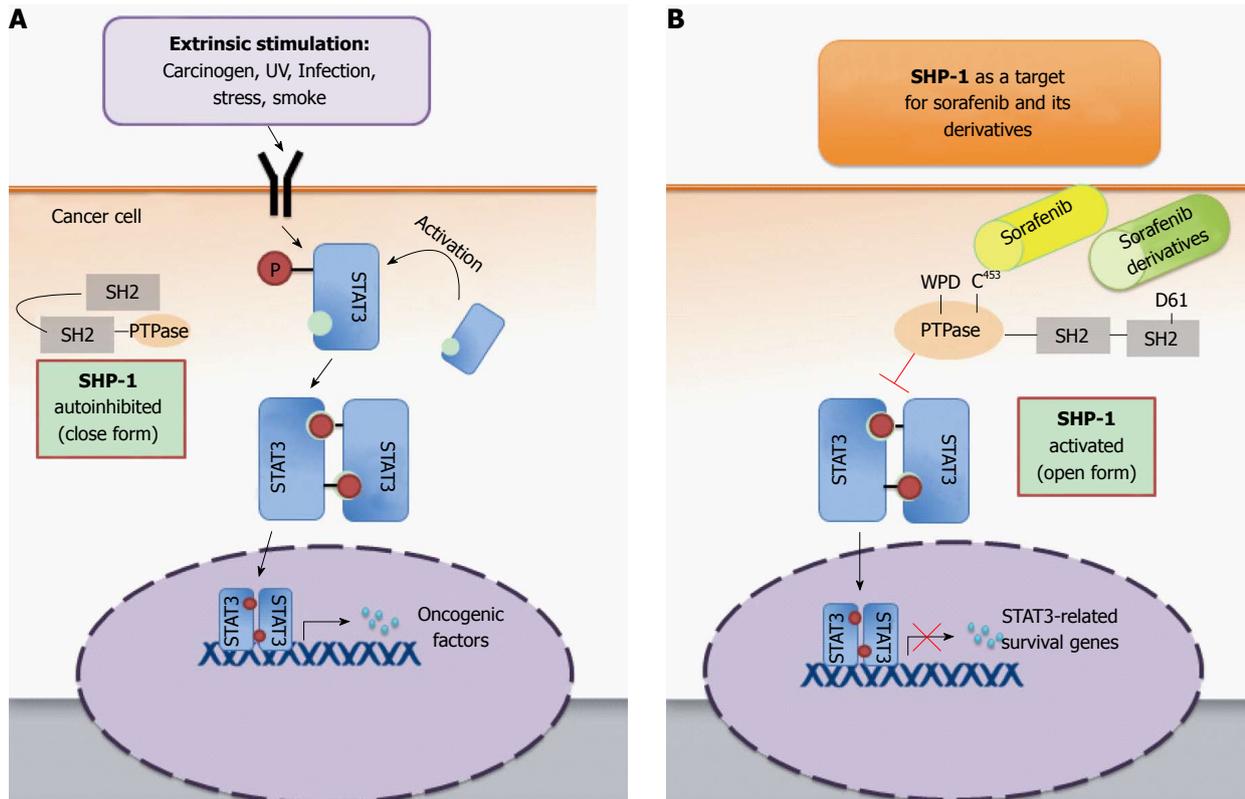
SHP-1, a member of the non-receptor family of PTPs, is comprised of two Src homology (SH) 2 domains that bind phosphotyrosine, a catalytic PTP domain, and a C-terminal tail. The activity of SHP-1 is closely related to its structural variability<sup>[51-53]</sup>. SHP-1 is autoinhibited when the N-terminal SH2 domain protrudes into the catalytic domain, blocking the active site of the catalytic pocket (closed form). The flexibility of the conserved WPD-loop, which contains an active site residue (Asp 421), also affects the catalytic activity of SHP-1<sup>[54]</sup>. Our group found that the anti-HCC effects of sorafenib are due to the formation of a critical salt bridge from the D61 residue in the N-SH2 domain, resulting in an "open" catalytic PTP domain and releasing the autoinhibition of SHP-1<sup>[49]</sup> (Figure 1). Furthermore, we found that several sorafenib derivatives, SC-1, SC-40 and SC-43, exhibit identical reactivation of SHP-1 and inhibition of STAT3 signaling in HCC cells. Excitingly, the anti-HCC potencies of these sorafenib derivatives were even more pronounced than those of sorafenib.

## OTHER STAT3 INHIBITORS

Various novel compounds have been developed to target STAT3 in different cancer types. Curcumin, a dihydroxyphenolic compound that downregulates JAK/STAT3 signaling by increasing the activity of PIAS3, has been tested in endothelial and ovarian cancer cells<sup>[27]</sup>. Cucurbitacin Q, a novel small molecule against STAT3 that does not inhibit JAK2, was shown to induce potent anti-cancer effects in lung and breast cancer cells with constitutively active STAT3<sup>[55]</sup>.

## CONCLUSION

Current data indicate that STAT3 is not only an important oncoprotein, but also a "druggable" target for various cancers, and reactivation of SHP-1 may be a feasible approach to target STAT3 and the STAT3-related



**Figure 1** Downregulation of signal transducer and activator 3 by reactivating Src homology region 2 domain-containing phosphatase 1 is an important anti-tumor property of sorafenib. Signal transducer and activator 3 (STAT3) is a key regulator that connects extrinsic carcinogenic stimulations and oncogenic signaling pathways (A). Sorafenib and its derivatives can inhibit STAT3 and STAT3-associated signaling pathways by reactivating SHP-1, a negative regulator of STAT3, in hepatocellular carcinoma cells (B).

signaling pathway. Sorafenib performs these functions in addition to its inhibition of multiple kinases. Knowledge of these kinase-independent properties of sorafenib provides an important foundation and suggests targeting of STAT3 and SHP-1 for future development of anti-cancer and HCC treatments.

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