**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 10205**

**Columns:** **MINIREVIEW**

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

Hung MH *et al.* Sorafenib inhibits STAT3 in HCC

Man-Hsin Hung, Wei-Tien Tai, Chung-Wai Shiau, Kuen-Feng Chen

**Man-Hsin Hung,** Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei 112, Taiwan

**Man-Hsin Hung,** Programin Molecular Medicine, School of Life Sciences, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan

**Wei-Tien Tai,** **Kuen-Feng Chen,** Department of Medical Research, National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, Taipei 100, Taiwan

**Chung-Wai Shiau,** Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei 112, Taiwan

**Author contributions:** Hung MH wrote the manuscript and generated the figures;

Tai WT and Shiau CW contributed to the writing and editing of the manuscript;

Chen KF generated the idea and designed the aims of this review and wrote the

manuscript.

**Correspondence to: Kuen-Feng Chen, MD, PhD,** Department of Medical Research, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei 100, Taiwan. kfchen1970@ntu.edu.tw

**Telephone:** +886-2-23123456 **Fax:** +886-2-23225329

**Received:** March 19, 2014 **Revised:** May 7, 2014

**Accepted:** June 12, 2014

**Published online:**

**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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**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.

Hung MH, Tai WT, Shiau CW, Chen KF. Downregulation of signal transducer and activator of transcription 3 by sorafenib: A novel mechanism for hepatocellular carcinoma therapy. *World J Gastroenterol* 2014; In press

**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[1,2]. 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 100,000 male inhabitants of eastern Asia[3].

 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[4]. 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[1]. 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[2,5]. 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[6,7], clinical trials testing several additional potent VEGFR inhibitors, such as sunitinib and brivanib, failed to show positive results[1,8,9]. The failures of these trials are thought to be multifactorial, including a lack of full understanding of the critical drivers of tumor progression[10]. 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[11]. STAT proteins, including STAT1–4, STAT5a, 5b and STAT6[12,13], 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[12] that govern various important cellular functions, such as cell differentiation, survival and immune response[14]. Among all the STAT proteins, STAT3 is particularly associated with oncogenesis[15,16].

***Regulation of STAT3 activity***

STAT3 is activated by cytokines, growth factors, carcinogens, stress, infection and radiation[14,17,18], 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[19-21]. 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[22,23].

 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[24]. 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[25]. 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[14,26,27].

***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[15,16,28]. He *et al*[29] 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[30-33]. Whereas activation of STAT3 by hepatitis C virus core protein or hepatitis B virus x protein promotes HCC growth[36,37], the downregulation of STAT3 reduces the growth of HCC *in vitro* and *in vivo*[34,35]. Furthermore, HCC development induced by diethylnitrosamine (DEN) in mice was prohibited when STAT3 signaling was reduced or conditionally knocked out[29,38,39]. 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[40-42]. 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[6,7]. 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 *vs* 7.9 mo with placebo)[6]. Later in the Asia-Pacific trial, Cheng and his colleagues 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[7].

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[43], 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[44]. Lyons *et al*[44] 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 effects 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-β, Fms-like tyrosine kinase-3, and fibroblast growth factor receptor-1[45-47].

 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[48]. 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[49,50].

***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[51-53]. 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[54]. 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[49] (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[27]. 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[55].

**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 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.

**REFERENCES**

1 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/s0140-6736(11)61347-0]

2 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

3 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

4 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

5 **Ding J**, Wang H. Multiple interactive factors in hepatocarcinogenesis. *Cancer Lett* 2014; **346**: 17-23 [PMID: 24374016 DOI: 10.1016/j.canlet.2013.12.024]

6 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

7 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/s1470-2045(08)70285-7]

8 **Llovet JM**, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; **31**: 3509-3516 [PMID: 23980090 DOI: 10.1200/jco.2012.47.3009]

9 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, Yang L, Lechuga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/jco.2012.45.8372]

10 **Llovet JM**, Hernandez-Gea V. Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design. *Clin Cancer Res* 2014; **20**: 2072-2079 [PMID: 24589894 DOI: 10.1158/1078-0432.ccr-13-0547]

11 **Akira S**, Nishio Y, Inoue M, Wang XJ, Wei S, Matsusaka T, Yoshida K, Sudo T, Naruto M, Kishimoto T. Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. *Cell* 1994; **77**: 63-71 [PMID: 7512451]

12 **Darnell JE**, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* 1994; **264**: 1415-1421 [PMID: 8197455]

13 **Darnell JE**. The JAK-STAT pathway: summary of initial studies and recent advances. *Recent Prog Horm Res* 1996; **51**: 391-403; discussion 403-4 [PMID: 8701087]

14 **Kamran MZ**, Patil P, Gude RP. Role of STAT3 in cancer metastasis and translational advances. *Biomed Res Int* 2013; **2013**: 421821 [PMID: 24199193 DOI: 10.1155/2013/421821]

15 **Buettner R**, Mora LB, Jove R. Activated STAT signaling in human tumors provides novel molecular targets for therapeutic intervention. *Clin Cancer Res* 2002; **8**: 945-954 [PMID: 11948098]

16 **Bowman T**, Garcia R, Turkson J, Jove R. STATs in oncogenesis. *Oncogene* 2000; **19**: 2474-2488 [PMID: 10851046 DOI: 10.1038/sj.onc.1203527]

17 **Takeda K**, Akira S. STAT family of transcription factors in cytokine-mediated biological responses. *Cytokine Growth Factor Rev* 2000; **11**: 199-207 [PMID: 10817963]

18 **Hirano T**, Ishihara K, Hibi M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene* 2000; **19**: 2548-2556 [PMID: 10851053 DOI: 10.1038/sj.onc.1203551]

19 **Garcia R**, Yu CL, Hudnall A, Catlett R, Nelson KL, Smithgall T, Fujita DJ, Ethier SP, Jove R. Constitutive activation of Stat3 in fibroblasts transformed by diverse oncoproteins and in breast carcinoma cells. *Cell Growth Differ* 1997; **8**: 1267-1276 [PMID: 9419415]

20 **Leaman DW**, Leung S, Li X, Stark GR. Regulation of STAT-dependent pathways by growth factors and cytokines. *FASEB J* 1996; **10**: 1578-1588 [PMID: 9002549]

21 **Yu CL**, Meyer DJ, Campbell GS, Larner AC, Carter-Su C, Schwartz J, Jove R. Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by the Src oncoprotein. *Science* 1995; **269**: 81-83 [PMID: 7541555]

22 **Chung J**, Uchida E, Grammer TC, Blenis J. STAT3 serine phosphorylation by ERK-dependent and -independent pathways negatively modulates its tyrosine phosphorylation. *Mol Cell Biol* 1997; **17**: 6508-6516 [PMID: 9343414]

23 **Yuan ZL**, Guan YJ, Chatterjee D, Chin YE. Stat3 dimerization regulated by reversible acetylation of a single lysine residue. *Science* 2005; **307**: 269-273 [PMID: 15653507 DOI: 10.1126/science.1105166]

24 **Chen W**, Daines MO, Khurana Hershey GK. Turning off signal transducer and activator of transcription (STAT): the negative regulation of STAT signaling. *J Allergy Clin Immunol* 2004; **114**: 476-89; quiz 490 [PMID: 15356544 DOI: 10.1016/j.jaci.2004.06.042]

25 **Han Y**, Amin HM, Franko B, Frantz C, Shi X, Lai R. Loss of SHP1 enhances JAK3/STAT3 signaling and decreases proteosome degradation of JAK3 and NPM-ALK in ALK+ anaplastic large-cell lymphoma. *Blood* 2006; **108**: 2796-2803 [PMID: 16825495 DOI: 10.1182/blood-2006-04-017434]

26 **Inagaki-Ohara K,** Kondo T, Ito M, Yoshimura A. SOCS, inflammation, and cancer. *JAKSTAT* 2013; **2**: e24053 [PMID: 24069550 DOI: 10.4161/jkst.24053]

27 **Saydmohammed M**, Joseph D, Syed V. Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells. *J Cell Biochem* 2010; **110**: 447-456 [PMID: 20235152 DOI: 10.1002/jcb.22558]

28 **Krasilnikov M**, Ivanov VN, Dong J, Ronai Z. ERK and PI3K negatively regulate STAT-transcriptional activities in human melanoma cells: implications towards sensitization to apoptosis. *Oncogene* 2003; **22**: 4092-4101 [PMID: 12821943 DOI: 10.1038/sj.onc.1206598]

29 **He G**, Yu GY, Temkin V, Ogata H, Kuntzen C, Sakurai T, Sieghart W, Peck-Radosavljevic M, Leffert HL, Karin M. Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. *Cancer Cell* 2010; **17**: 286-297 [PMID: 20227042 DOI: 10.1016/j.ccr.2009.12.048]

30 **Sinibaldi D**, Wharton W, Turkson J, Bowman T, Pledger WJ, Jove R. Induction of p21WAF1/CIP1 and cyclin D1 expression by the Src oncoprotein in mouse fibroblasts: role of activated STAT3 signaling. *Oncogene* 2000; **19**: 5419-5427 [PMID: 11114718 DOI: 10.1038/sj.onc.1203947]

31 **Aoki Y**, Feldman GM, Tosato G. Inhibition of STAT3 signaling induces apoptosis and decreases survivin expression in primary effusion lymphoma. *Blood* 2003; **101**: 1535-1542 [PMID: 12393476 DOI: 10.1182/blood-2002-07-2130]

32 **Catlett-Falcone R**, Landowski TH, Oshiro MM, Turkson J, Levitzki A, Savino R, Ciliberto G, Moscinski L, Fernández-Luna JL, Nuñez G, Dalton WS, Jove R. Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity* 1999; **10**: 105-115 [PMID: 10023775]

33 **Wang T**, Niu G, Kortylewski M, Burdelya L, Shain K, Zhang S, Bhattacharya R, Gabrilovich D, Heller R, Coppola D, Dalton W, Jove R, Pardoll D, Yu H. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. *Nat Med* 2004; **10**: 48-54 [PMID: 14702634 DOI: 10.1038/nm976]

34 **Zhang JF**, He ML, Fu WM, Wang H, Chen LZ, Zhu X, Chen Y, Xie D, Lai P, Chen G, Lu G, Lin MC, Kung HF. Primate-specific microRNA-637 inhibits tumorigenesis in hepatocellular carcinoma by disrupting signal transducer and activator of transcription 3 signaling. *Hepatology* 2011; **54**: 2137-2148 [PMID: 21809363 DOI: 10.1002/hep.24595]

35 **Avella DM**, Li G, Schell TD, Liu D, Zhang SS, Lou X, Berg A, Kimchi ET, Tagaram HR, Yang Q, Shereef S, Garcia LS, Kester M, Isom HC, Rountree CB, Staveley-O'Carroll KF. Regression of established hepatocellular carcinoma is induced by chemoimmunotherapy in an orthotopic murine model. *Hepatology* 2012; **55**: 141-152 [PMID: 21898502 DOI: 10.1002/hep.24652]

36 **Wang C**, Yang W, Yan HX, Luo T, Zhang J, Tang L, Wu FQ, Zhang HL, Yu LX, Zheng LY, Li YQ, Dong W, He YQ, Liu Q, Zou SS, Lin Y, Hu L, Li Z, Wu MC, Wang HY. Hepatitis B virus X (HBx) induces tumorigenicity of hepatic progenitor cells in 3,5-diethoxycarbonyl-1,4-dihydrocollidine-treated HBx transgenic mice. *Hepatology* 2012; **55**: 108-120 [PMID: 21932402 DOI: 10.1002/hep.24675]

37 **Machida K**, Tsukamoto H, Liu JC, Han YP, Govindarajan S, Lai MM, Akira S, Ou JH. c-Jun mediates hepatitis C virus hepatocarcinogenesis through signal transducer and activator of transcription 3 and nitric oxide-dependent impairment of oxidative DNA repair. *Hepatology* 2010; **52**: 480-492 [PMID: 20683948 DOI: 10.1002/hep.23697]

38 **Naugler WE**, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007; **317**: 121-124 [PMID: 17615358 DOI: 10.1126/science.1140485]

39 **Wang H**, Lafdil F, Wang L, Park O, Yin S, Niu J, Miller AM, Sun Z, Gao B. Hepatoprotective versus oncogenic functions of STAT3 in liver tumorigenesis. *Am J Pathol* 2011; **179**: 714-724 [PMID: 21684247 DOI: 10.1016/j.ajpath.2011.05.005]

40 **Park O**, Wang H, Weng H, Feigenbaum L, Li H, Yin S, Ki SH, Yoo SH, Dooley S, Wang FS, Young HA, Gao B. In vivo consequences of liver-specific interleukin-22 expression in mice: Implications for human liver disease progression. *Hepatology* 2011; **54**: 252-261 [PMID: 21465510 DOI: 10.1002/hep.24339]

41 **Riehle KJ**, Campbell JS, McMahan RS, Johnson MM, Beyer RP, Bammler TK, Fausto N. Regulation of liver regeneration and hepatocarcinogenesis by suppressor of cytokine signaling 3. *J Exp Med* 2008; **205**: 91-103 [PMID: 18158318 DOI: 10.1084/jem.20070820]

42 **Bard-Chapeau EA**, Li S, Ding J, Zhang SS, Zhu HH, Princen F, Fang DD, Han T, Bailly-Maitre B, Poli V, Varki NM, Wang H, Feng GS. Ptpn11/Shp2 acts as a tumor suppressor in hepatocellular carcinogenesis. *Cancer Cell* 2011; **19**: 629-639 [PMID: 21575863 DOI: 10.1016/j.ccr.2011.03.023]

43 **Lencioni R**, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, Ladrón de Guevara L, Papandreou C, Sanyal AJ, Takayama T, Yoon SK, Nakajima K, Cihon F, Heldner S, Marrero JA. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. *Int J Clin Pract* 2012; **66**: 675-683 [PMID: 22698419 DOI: 10.1111/j.1742-1241.2012.02940.x]

44 **Wilhelm S**, Chien DS. BAY 43-9006: preclinical data. *Curr Pharm Des* 2002; **8**: 2255-2257 [PMID: 12369853]

45 **Wilhelm SM**, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; **64**: 7099-7109 [PMID: 15466206 DOI: 10.1158/0008-5472.can-04-1443]

46 **Liu L**, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, Wilhelm S, Lynch M, Carter C. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006; **66**: 11851-11858 [PMID: 17178882 DOI: 10.1158/0008-5472.can-06-1377]

47 **Auclair D**, Miller D, Yatsula V, Pickett W, Carter C, Chang Y, Zhang X, Wilkie D, Burd A, Shi H, Rocks S, Gedrich R, Abriola L, Vasavada H, Lynch M, Dumas J, Trail PA, Wilhelm SM. Antitumor activity of sorafenib in FLT3-driven leukemic cells. *Leukemia* 2007; **21**: 439-445 [PMID: 17205056 DOI: 10.1038/sj.leu.2404508]

48 **Chen KF**, Tai WT, Liu TH, Huang HP, Lin YC, Shiau CW, Li PK, Chen PJ, Cheng AL. Sorafenib overcomes TRAIL resistance of hepatocellular carcinoma cells through the inhibition of STAT3. *Clin Cancer Res* 2010; **16**: 5189-5199 [PMID: 20884624 DOI: 10.1158/1078-0432.ccr-09-3389]

49 **Tai WT**, Shiau CW, Chen PJ, Chu PY, Huang HP, Liu CY, Huang JW, Chen KF. Discovery of novel Src homology region 2 domain-containing phosphatase 1 agonists from sorafenib for the treatment of hepatocellular carcinoma. *Hepatology* 2014; **59**: 190-201 [PMID: 23908138 DOI: 10.1002/hep.26640]

50 **Tai WT**, Cheng AL, Shiau CW, Huang HP, Huang JW, Chen PJ, Chen KF. Signal transducer and activator of transcription 3 is a major kinase-independent target of sorafenib in hepatocellular carcinoma. *J Hepatol* 2011; **55**: 1041-1048 [PMID: 21354226 DOI: 10.1016/j.jhep.2011.01.047]

51 **Yang J**, Liang X, Niu T, Meng W, Zhao Z, Zhou GW. Crystal structure of the catalytic domain of protein-tyrosine phosphatase SHP-1. *J Biol Chem* 1998; **273**: 28199-28207 [PMID: 9774441]

52 **Yang J**, Liu L, He D, Song X, Liang X, Zhao ZJ, Zhou GW. Crystal structure of human protein-tyrosine phosphatase SHP-1. *J Biol Chem* 2003; **278**: 6516-6520 [PMID: 12482860 DOI: 10.1074/jbc.M210430200]

53 **Wang W**, Liu L, Song X, Mo Y, Komma C, Bellamy HD, Zhao ZJ, Zhou GW. Crystal structure of human protein tyrosine phosphatase SHP-1 in the open conformation. *J Cell Biochem* 2011; **112**: 2062-2071 [PMID: 21465528 DOI: 10.1002/jcb.23125]

54 **Wu C**, Sun M, Liu L, Zhou GW. The function of the protein tyrosine phosphatase SHP-1 in cancer. *Gene* 2003; **306**: 1-12 [PMID: 12657462]

55 **Sun J**, Blaskovich MA, Jove R, Livingston SK, Coppola D, Sebti SM. Cucurbitacin Q: a selective STAT3 activation inhibitor with potent antitumor activity. *Oncogene* 2005; **24**: 3236-3245 [PMID: 15735720 DOI: 10.1038/sj.onc.1208470]

**P-Reviewer:** Bloomston M, Takigawa N **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**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).

A



B

 