The Korean Journal of Hepatology 2010;16:418-419
DOI: 10.3350/kjhep.2010.16.4.418

The effect of sorafenib on hepatic stellate cells: implication of its effect on tumor microenvironment

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New insights into the antifibrotic effects of sorafenib on hepatic stellate cells and liver fibrosis.

Wang Y, Gao J, Zhang D, Zhang J, Ma J, Jiang H.
J hepatol 2010;53:132-144.

Sorafenib is a multiple receptor tyrosine kinase inhibitor that has been shown to improve the survival of patients with advanced hepatocellular carcinoma (HCC).[1,2] It acts by blocking the receptor tyrosine kinases such as vascular endothelial growth factor receptors (VEGFR), platelet derived growth factor receptor (PDGFR), c-Kit, fibroblast growth factor receptor-1, and the serine/threonine kinase RAF, thereby repressing cell proliferation and angiogenesis.[3,4] The drug is currently considered as the standard of care in patients with advanced HCC and preserved liver function.[5] Unfortunately, majority of patients with advanced HCC still die from the disease despite of the sorafenib treatment. In order to satisfy the unmet need in treating advanced HCC, additional investigation is required to clarify the molecular pathogenesis of HCC. Understanding the mechanism of action of sorafenib, both on tumor and non-tumor tissue, would be a step forward.

Multiple kinases that are suppressed by sorafenib not only involve in the survival of tumor cells themselves but also that of other cells surrounding the tumor tissue. There have been growing evidences that this surrounding tissue, so called the tumor microenvironments, would play an important role in tumoregenesis, tumor invasion and metastasis.[6,7] The tumor microenvironments of HCC include cells such as hepatic stellate cells (HSCs) and immune cells, growth factors, proteolytic enzymes, extracellular matrix and inflammatory cytokines.

HSCs are activated in response to liver damage. The repeated injury would result in liver fibrosis.[8] In addition, activated HSCs may infiltrate the stroma of liver tumors and localize around tumor sinusoids, fibrous septa and capsules.[9] It has been reported that the media collected from HSCs induced proliferation and migration of HCC cells, cultured in monolayers. It also has been demonstrated that simultaneous in vivo implantation of HSCs and HCC cells into nude mice promoted tumor growth and invasiveness when necrosis was inhibited.[10]

The study by Wang et al[11]reported the effect of sorafenib on HSCs in vitro and liver fibrosis in vivo. On two separate liver fibrosis animal models, one induced by bile duct ligation and the other chemically induced by intraperitoneal dimethylnitrosamine (DMN), sorafenib attenuated liver fibrosis. Liver fibrosis was histologically evaluated by Masson's trichrome collagen staining and quantification of collagen production. However, the behavior of HSCs upon sorafenib treatment in vivo was not fully investigated in this particular study. The effect of sorafenib on HSC proliferation and apoptosis were shown only on HSC cell lines. Although the assumption could be made that the anti-fibrotic effect was caused by sorafenib on HSCs, being the key player in liver fibrosis, more solid evidence would be preferred. This evi-

Keywords: Sorafenib; Hepatocellular carcinoma; Stellate cell

Abbreviations: HCC, hepatocellular carcinoma; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet derived growth factor receptor; HSC, hepatic stellate cell; DMN, dimethylnitrosamine; ALT, alanine aminotransferase

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dence came from the study by Hennenberg et al[12] that was recently published. The study showed the decreased number of α-smooth muscle actin positive cells in bile duct ligated rats after sorafenib administration.[12]

Both Wang and Hennenberg studies emphasized the role of sorafenib as antifibrotic agent. These studies support the previous investigations reporting the beneficial effect of sorafenib on portal hypertension.[13,14] However, translation and clinical application of these results in treating portal hypertension and cirrhosis still have to undergo very carefully. In vivo studies, including the one performed by Wang Y et al, showed aggravation in liver parameters such as serum alanine aminotransferase (ALT) by certain concentration of sorafenib. Instead, the effect of sorafenib on HSCs rather implies that sorafenib not only suppresses the tumor cells themselves but also attenuates the tumor microenvironments that might have cross-talk with the cancer cells. Evaluating the effect of sorafenib on HSCs surrounding HCC would provide better perspective on this. In addition, understanding the behavior of sorafenib on the tissue surrounding the tumor might give more clues for pathogenesis of HCC thus better strategy against HCC. There has been growing number of reports over the recent years that emphasized the role of tumor microenvironments. It appears that tumor cells, once thought to be autonomous, seem to depend on angiogenesis, inflammatory cells and fibroblasts.[15-17] Therefore it would be ideal if the treatment were to target tumor-microenvironment interaction that stimulated tumor progression, invasion and metastasis as well as hepatocarcinogenesis. Further studies evaluating how sorafenib meet this goal would be a great resource in developing new drugs that could be used alone or in combination with sorafenib.

In summary, evidences that show anti-fibrotic effect of sorafenib through suppressing HSCs has been reported. Implication and use of this information may need further contemplation.

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