Biomedicine & Pharmacotherapy 88 (2017) 459–468

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Review

Sorafenib: A potential therapeutic drug for hepatic fibrosis and its outcomes

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ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 17 January 2017
Accepted 17 January 2017

Keywords:
Hepatic fibrosis
Sorafenib
Therapeutic drug
Liver injury
Liver microenvironment

ABSTRACT

Hepatic fibrosis is a common response to liver injury that occurs in almost all liver diseases and is characterized by an excessive deposition of extracellular matrix, which can cause hepatic dysfunction and develop into cirrhosis. There is no curative treatment except liver transplantation and few treatments have been thoroughly validated in the clinic or commercialized as a therapy. Recently, sorafenib, an FDA approved molecular targeted drug for the treatment of advanced hepatocellular and renal cell carcinomas, has been reported to exert anti-fibrotic effects in liver fibrosis. Animal models showed that sorafenib ameliorated intrahepatic vascular resistance, reduced portal hypertension, and reduced intrahepatic fibrosis, inflammation and angiogenesis. In this review, we highlight the potential molecular, cellular, microenvironmental mechanisms underlying the antifibrotic effects of sorafenib in fibrotic liver disease, and briefly discuss the potential of sorafenib for hepatic fibrogenesis and major complications in clinical treatments. There is a long way to go before sorafenib can be applied in preclinical practice and clinical therapy of liver fibrosis. Further studies are required to clarify its anti-fibrotic role, effective dose, and side effects.

Contents

Abbreviations: NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis3; ECM, Extracellular matrix; VEGF-R, Vascular endothelial growth factor receptor; PDGF-R, Platelet-derived growth factor receptor; c-KIT, c-kit proto-oncogene protein; FLT-3, FMS-like tyrosine kinase 3; HSC, Hepatic stellate cells; HCs, Hepatocytes; LECs, Liver sinusoidal endothelial cells; TGF-b, Transforming growth factor b; EMT, Epithelial-mesenchymal transition; AML12 cells, Mouse HCs; STAT3, Signal transducer and activator of transcription 3; JAK, Janus tyrosine kinases; BDL, Bile duct ligation; PDGF-BB, Platelet-derived growth factor subunit B homodimer; NASH, Nonalcoholic steatohepatitis; RCR, Respiratory control ratio; PGC-1, The transcriptional coactivator PPAR-g coactivator-1; PPAR-a, Peroxisome proliferator activated receptor alpha; NO, Nitric oxide; MVD, Microvascular density; vWF, Willebrand Factor; PSV/SV, Post-sinusoidal/sinusoidal venules; RAAS, Rennin–angiotensin–aldosterone system; HE, Hepatic encephalopathy.

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http://dx.doi.org/10.1016/j.biopha.2017.01.107
0753-3322/

1. Introduction

Hepatic fibrosis is a highly conserved response to liver injury that occurs in almost all types of liver disease [1]. The initial stage of liver fibrosis is commonly non-alcoholic fatty liver disease (NAFLD), which often found in the absence of significant alcohol consumption, viral infection, or autoimmune or drug-related liver injury [2]. NAFLD ranges from hepatic fat accumulation to non-alcoholic steatohepatitis (NASH). Approximately one third of the overall population suffer from NAFLD [3]. If NAFLD is not treated in time, it will progress to fibrosis [4]. Hepatic fibrosis is characterized by an excessive deposition of extracellular matrix (ECM) that can cause hepatic dysfunction, can develop into cirrhosis. There is no curative treatment except liver transplantation [5,6]. During this clinicopathological process, increased incidence of liver cancer also threatens cirrhotic patients [7]. Although anti-fibrotic activity has been confirmed *in vivo* and *in vitro*, few treatments have been thoroughly validated in the clinic or commercialized as a therapy for hepatic fibrosis. Thus, physicians and scientists are actively seeking curative interventions in the fibrotic process.

Recently, sorafenib has been reported to exert anti-fibrotic effects in liver fibrosis. Sorafenib is a multikinase inhibitor that inhibits both cell surface tyrosine kinase receptors and intracellular serine/threonine kinases in the Ras/MAPK cascade [8–10]. Sorafenib can inhibit receptor tyrosine kinases including vascular endothelial growth factor receptor (VEGF-R), platelet-derived growth factor receptor (PDGF-R), c-kitproto-oncogene protein (c-KIT), FMS-like tyrosine kinase 3 (FLT-3), and RET; and downstream intracellular serine/threonine kinases, such as Raf-1, mutant B-Raf, and wild-type B-Raf [9,10]. Sorafenib is an FDA approved molecular targeted drug for the treatment of advanced hepatocellular and renal cell carcinomas [11–13]. Inhibiting the pathways of RAF/MEK/ERK, decreasing tumor cell proliferation and angiogenesis, and increasing tumor cell apoptosis all contribute to the effects of sorafenib [14].

In addition to its established clinical benefits for patients with a broad range of tumor types, recent preclinical studies have demonstrated that sorafenib could be used to treat liver cirrhosis [15–17]. In rats, sorafenib ameliorated intrahepatic vascular resistance, and thus reduced portal hypertension, a major complication of fibrosis [15,17]. Mejias et al. [15] first reported that sorafenib reduced intrahepatic fibrosis, inflammation, angiogenesis and portal hypertension in a cirrhotic rat model. Subsequent studies demonstrated that sorafenib also reduced the proliferation of hepatic stellate cells (HSC) and inhibited the synthesis of fibrogenesis-related proteins and the ECM [18–20].

Based on these findings in animal models, sorafenib could be considered a potential anti-fibrotic drug. Nevertheless, we do not have a clear understanding of the mechanisms of sorafenib in ameliorating hepatic fibrosis. In this review, we will highlight the potential molecular, cellular, microenvironmental mechanisms underlying the anti-fibrotic effects of sorafenib in fibrotic liver disease, and briefly discuss the potential of sorafenib for hepatic fibrogenesis and major complications in clinical treatments.

2. Liver cell types and potential molecular signaling pathways that link fibrosis

The progression of hepatic fibrosis is a complex process, involving parenchymal and non-parenchymal cells, including hepatocytes (HCs), liver sinusoidal endothelial cells (LECs), HSCs, and Kupffer cells [21]. These cells are important to the fibrotic process and complicated interplay amongst hepatic cell lineages occurs during fibrogenesis [22,23]. Recently, attention has gradually shifted towards liver cells during regulation of the progression or regression of hepatic fibrosis [24]. Currently, the various beneficial effects of sorafenib have been reported on different cells in the process of liver fibrosis (Fig. 1).

2.1. HCs

HCs are the major victims of liver fibrosis [25]. Cellular components released from dying cells induce inflammatory and fibrogenic responses; therefore, damaged HCs play a key role in the pathogenesis of inflammation and fibrosis in the liver. However, whether HCs affect the development and progression of liver fibrosis through the epithelial to mesenchymal transition (EMT) remains controversial [26]. Zeisberg et al. [27] reported that HCs could be induced to undergo EMT by transforming growth factor β (TGF-β), and are involved in the accumulation of activated fibroblasts in the fibrotic liver. Nevertheless, another study showed that *in vivo*, HCs did not acquire a mesenchymal phenotype through EMT to produce the ECM in liver fibrosis [28]. Therefore, we need more evidence of the role of HCs in the process of liver fibrosis.