World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 February 14; 30(6): 607-609

DOI: 10.3748/wjg.v30.i6.607

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Angiotensin-converting enzyme 2 alleviates liver fibrosis through the renin-angiotensin system

Bai-Wei Zhao, Ying-Jia Chen, Ruo-Peng Zhang, Yong-Ming Chen, Bo-Wen Huang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Buechler C, Germany; Ferraioli G, Italy

Received: October 31, 2023
Peer-review started: October 31, 2023
First decision: December 6, 2023
Revised: December 17, 2023
Accepted: January 15, 2024
Article in press: January 15, 2024
Published online: February 14, 2024

Bai-Wei Zhao, Ruo-Peng Zhang, Yong-Ming Chen, Bo-Wen Huang, Department of Gastric Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou 510060, Guangdong Province, China

Ying-Jia Chen, Health Science Center, Peking University, Beijing 100191, China

Corresponding author: Bo-Wen Huang, MD, Professor, Department of Gastric Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, No. 651 Dongfeng East Road, Yuexiu District, Guangzhou 510060, Guangdong Province, China. huangbw1@sysucc.org.cn

Abstract

The present letter to the editor is related to the study titled 'Angiotensin-converting enzyme 2 improves liver fibrosis in mice by regulating autophagy of hepatic stellate cells'. Angiotensin-converting enzyme 2 can alleviate liver fibrosis by regulating autophagy of hepatic stellate cells and affecting the renin-angiotensin system.

Key Words: Angiotensin-converting enzyme 2; Hepatic stellate cells; Liver fibrosis; Angiotensin II; Angiotensin 1-7; Renin-angiotensin system

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This letter to the editor adds to the ongoing conversation regarding the involvement of angiotensin-converting enzyme 2 (ACE2) in liver fibrosis from the perspective of its effect on the renin-angiotensin system (RAS). The major highlight of this letter is the discussion of the role of ACE2 in regulating liver fibrosis through RAS beyond the pathway studied in the article titled 'Angiotensin-converting enzyme 2 improves liver fibrosis in mice by regulating autophagy of hepatic stellate cells'.

Citation: Zhao BW, Chen YJ, Zhang RP, Chen YM, Huang BW. Angiotensin-converting enzyme 2 alleviates liver fibrosis through the renin-angiotensin system. *World J Gastroenterol* 2024; 30(6): 607-609
URL: https://www.wjgnet.com/1007-9327/full/v30/i6/607.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i6.607

TO THE EDITOR

In the study of Wu *et al*[1], the authors concluded that the overexpression of angiotensin-converting enzyme 2 (ACE2) can regulate hepatic stellate cells (HSCs) autophagy by the adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin pathway to inhibit the activation of HSC and promote HSC apoptosis, thereby alleviating liver fibrosis and hepatic sinusoidal remodeling.

Hepatic fibrosis is caused by a sustained normal wound healing response, resulting in an abnormal persistence of the production and deposition of connective tissue[2]. Liver fibrogenesis and cirrhosis are usually accompanied by severe complications, such as portal hypertension, liver failure, and an increased risk of hepatocellular carcinoma[3].

HSCs play an essential role in the pathogenesis and development of hepatic fibrosis. In healthy livers, HSCs are situated in the perisinusoidal space, also known as the space of Disse, between hepatocytes and liver sinusoidal endothelial cells[4]. However, in chronic liver diseases, HSCs are stimulated by damaged hepatocytes and transform into a myofibroblastic phenotype[5]. Upon activation, HSCs exhibit increased α-smooth muscle actin expression[6]. At the same time, HSCs produce a large number of extracellular matrix (ECM) proteins, such as collagens I and III, as well as fibronectin[6]. Excess fibrous ECM proteins are deposited in the space of Disse of hepatic sinusoids, ultimately resulting in liver fibrosis[7]. Moreover, the contraction of HSCs increases the pressure on hepatic sinusoids. This can cause stenosis, thereby causing and exacerbating portal hypertension[8].

Liver fibrosis has high rates of morbidity and mortality throughout the world. However, there are still no effective prevention and therapy methods for liver fibrosis currently. The findings of Wu *et al*[1]. indicate new directions for improving hepatic sinusoidal remodeling and give a new theoretical foundation for the preventive and targeted treatment of hepatic fibrogenesis and portal hypertension. However, further research is needed to enable its clinical application.

In addition to the pathway expounded by Wu *et al*[1], ACE2 can affect liver fibrosis through the renin-angiotensin system (RAS). In order to induce overexpression of ACE2 in a mouse model of hepatic fibrogenesis, Wu *et al*[1] injected a liver-specific recombinant adeno-associated virus ACE2 vector (rAAV2/8-ACE2) into the mice[1]. Then, Wu *et al*[1] measured the serum levels of angiotensin (Ang) II and Ang 1-7 and found that the level of Ang II decreased while the level of Ang 1-7 increased[1]. Osterreicher *et al*[9] showed that ACE2, a critical negative regulator of the RAS, can degrade Ang II and form Ang 1-7, thereby limiting fibrosis. In chronic liver injury models, loss of ACE2 activity exacerbates liver fibrosis, while the administration of recombinant ACE2 shows therapeutic potential.

RAS is a significant endocrine system that regulates vascular tension, maintains blood pressure homeostasis, and keeps water and electrolyte balance[10]. In the classic RAS pathway, juxtaglomerular cells of renal afferent arterioles secrete renin, which can cleave angiotensinogen (AGT), a liver-derived precursor peptide, to produce Ang I, a decapeptide[9]. AGT is produced in large quantities in liver cells and is the primary source of circulating AGT in healthy conditions[11]. Therefore, decreasing the secretion of AGT may be an effective strategy for treating liver fibrosis.

One of the RAS axes involves an angiotensin-converting enzyme (ACE)[12]. Through ACE action, Ang I, a main effector peptide of the RAS, is hydrolyzed to form Ang II, an octapeptide additionally[9]. Kurikawa *et al*[13] showed that HSCs exhibit significantly enhanced proliferation and increased collagen synthesis following Ang II binding to its receptor, which plays a vital role in the aggravation of hepatic fibrosis. The serum and tissue levels of Ang II were elevated in ACE2 knockout mice[14]. Ang II type 1 receptor (AT1R), which can be expressed in activated HSCs, is the main effector mediating the effects of Ang II[12]. AT1R blockers can inhibit the proliferation of HSC and improve hepatic fibrosis[13]. Ang II activates AT1R, which causes Ras homolog gene family member A to activate Rho-kinase. This up-regulates the phosphorylation and contraction of the myosin light chain, which participates in developing hepatic fibrosis and portal hypertension[15]. Furthermore, ACE inhibitors can alleviate the progression of hepatic fibrosis[16].

Another axis of RAS is the hydrolysis of Ang II to Ang 1-7 mediated by ACE2[12]. Ang 1-7 is an active peptide and a vasodilator, exerting its effects through binding to the G-protein coupled receptor, Mas[10]. Mas is the main effector of Ang 1-7, conveying vasodilation, anti-proliferation, anti-inflammation, and anti-fibrosis effects. In different models of human diseases, activation of the ACE2/Ang 1-7/Mas axis inhibits inflammatory cell function and fibrogenesis[12]. Furthermore, Ang 1-7 can activate the production of nitric oxide and endothelial nitric oxide synthase in endothelial cells [10].

The pathway described in the study of Wu *et al*[1] is not entirely independent of the pathway associated with RAS. When the balance between the classical RAS arm (ACE/Ang II/AT1R) and the protective arm (ACE2/Ang 1-7/Mas receptor) is disrupted, the expression of ACE and AT1R is inhibited, and the expression of ACE2 and Mas is increased at the same time under the action of activated AMPK. Following the up-regulation of ACE2, the metabolism of Ang II to Ang 1-7 is increased; activated AMPK suppresses the classical RAS pathway and elevates the protective arm, maintaining the balance of RAS[17].

FOOTNOTES

Co-first authors: Bai-Wei Zhao and Ying-Jia Chen.

Author contributions: Zhao BW and Chen YJ share the first author; Huang BW and Chen YJ designed research; Zhao BW and Zhang RP performed research; Chen YJ and Chen YM wrote the letter; Huang BW and Zhao BW revised the letter.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Bo-Wen Huang 0000-0003-4588-659X.

S-Editor: Li L
L-Editor: A
P-Editor: Li L

REFERENCES

1 **Wu Y**, Yin AH, Sun JT, Xu WH, Zhang CQ. Angiotensin-converting enzyme 2 improves liver fibrosis in mice by regulating autophagy of hepatic stellate cells. *World J Gastroenterol* 2023; **29**: 4975-4990 [PMID: 37732000 DOI: 10.3748/wjg.v29.i33.4975]
2 **Schuppan D**, Afdhal NH. Liver cirrhosis. *Lancet* 2008; **371**: 838-851 [PMID: 18328931 DOI: 10.1016/S0140-6736(08)60383-9]
3 **Iredale JP**. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. *J Clin Invest* 2007; **117**: 539-548 [PMID: 17332881 DOI: 10.1172/JCI30542]
4 **Deleve LD**, Wang X, Guo Y. Sinusoidal endothelial cells prevent rat stellate cell activation and promote reversion to quiescence. *Hepatology* 2008; **48**: 920-930 [PMID: 18613151 DOI: 10.1002/hep.22351]
5 **Tsuchida T**, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 397-411 [PMID: 28487545 DOI: 10.1038/nrgastro.2017.38]
6 **Sui M**, Jiang X, Chen J, Yang H, Zhu Y. Magnesium isoglycyrrhizinate ameliorates liver fibrosis and hepatic stellate cell activation by regulating ferroptosis signaling pathway. *Biomed Pharmacother* 2018; **106**: 125-133 [PMID: 29957462 DOI: 10.1016/j.biopha.2018.06.060]
7 **Dewidar B**, Meyer C, Dooley S, Meindl-Beinker AN. TGF-β in Hepatic Stellate Cell Activation and Liver Fibrogenesis-Updated 2019. *Cells* 2019; **8** [PMID: 31718044 DOI: 10.3390/cells8111419]
8 **Iwakiri Y**, Trebicka J. Portal hypertension in cirrhosis: Pathophysiological mechanisms and therapy. *JHEP Rep* 2021; **3**: 100316 [PMID: 34337369 DOI: 10.1016/j.jhepr.2021.100316]
9 **Osterreicher CH**, Taura K, De Minicis S, Seki E, Penz-Osterreicher M, Kodama Y, Kluwe J, Schuster M, Oudit GY, Penninger JM, Brenner DA. Angiotensin-converting-enzyme 2 inhibits liver fibrosis in mice. *Hepatology* 2009; **50**: 929-938 [PMID: 19650157 DOI: 10.1002/hep.23104]
10 **Iwakiri Y**, Shah V, Rockey DC. Vascular pathobiology in chronic liver disease and cirrhosis - current status and future directions. *J Hepatol* 2014; **61**: 912-924 [PMID: 24911462 DOI: 10.1016/j.jhep.2014.05.047]
11 **Paizis G**, Cooper ME, Schembri JM, Tikellis C, Burrell LM, Angus PW. Up-regulation of components of the renin-angiotensin system in the bile duct-ligated rat liver. *Gastroenterology* 2002; **123**: 1667-1676 [PMID: 12404241 DOI: 10.1053/gast.2002.36561]
12 **Simões e Silva AC**, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br J Pharmacol* 2013; **169**: 477-492 [PMID: 23488800 DOI: 10.1111/bph.12159]
13 **Kurikawa N**, Suga M, Kuroda S, Yamada K, Ishikawa H. An angiotensin II type 1 receptor antagonist, olmesartan medoxomil, improves experimental liver fibrosis by suppression of proliferation and collagen synthesis in activated hepatic stellate cells. *Br J Pharmacol* 2003; **139**: 1085-1094 [PMID: 12871826 DOI: 10.1038/sj.bjp.0705339]
14 **Crackower MA**, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature* 2002; **417**: 822-828 [PMID: 12075344 DOI: 10.1038/nature00786]
15 **Trebicka J**, Hennenberg M, Laleman W, Shelest N, Biecker E, Schepke M, Nevens F, Sauerbruch T, Heller J. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. *Hepatology* 2007; **46**: 242-253 [PMID: 17596891 DOI: 10.1002/hep.21673]
16 **Jonsson JR**, Clouston AD, Ando Y, Kelemen LI, Horn MJ, Adamson MD, Purdie DM, Powell EE. Angiotensin-converting enzyme inhibition attenuates the progression of rat hepatic fibrosis. *Gastroenterology* 2001; **121**: 148-155 [PMID: 11438504 DOI: 10.1053/gast.2001.25480]
17 **Liu J**, Li X, Lu Q, Ren D, Sun X, Rousselle T, Li J, Leng J. AMPK: a balancer of the renin-angiotensin system. *Biosci Rep* 2019; **39** [PMID: 31413168 DOI: 10.1042/BSR20181994]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2024 Baishideng Publishing Group Inc. All rights reserved.