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

Zhao *et al*. Effect of ACE2 on RAS

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**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

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**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’.

**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].

**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]

**Footnotes**

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