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

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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'.

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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

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