Chapter 12

Local Renin-Angiotensin System at Liver and Crosstalk with Hepatic Diseases

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Additional information is available at the end of the chapter

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Abstract

The systemic renin-angiotensin system mainly regulates blood pressure and maintains kidney function. Recent studies have realized that renin-angiotensin system (RAS) has been found in many tissues, such as heart, liver, and kidney. Although RAS in heart and kidney has been well documented, the RAS in the liver has been evaluated in a few studies. Therefore, this chapter will be assessed it. Based on findings, RAS in the liver has presented almost all of its components, such as angiotensin-I (Ang-I), angiotensin-II (Ang-II), angiotensin-converting enzyme (ACE), angiotensin type-1 receptor (AT1), angiotensin type-2 receptor (AT2), named as classical RAS. Expect these components, the local RAS has had alternative pathway components, including angiotensin-converting enzyme 2 (ACE2) and chymase. Classical RAS has an opposite effect of alternative RAS. Although these local RAS might not be such a crucial for the tissue, it could be a more vital function under pathophysiologic conditions. The chapter the local RAS in the liver the under both physiologic and pathophysiologic conditions is highlighted.

Keywords: angiotensin-II, angiotensin-converting enzyme 2, local renin-angiotensin system, liver pathologies

1. Introduction

Although early studies focused on the systemic renin-angiotensin system (RAS) which are important endocrine cascade to regulate the salt-water balance, scientists have recognized there is one more RAS, called as local or tissue RAS except for classical systemic effects [1]. The first recognition of local RAS has been reported that the in dog's brain the renin was found [2]. Then, various tissues, such as the heart, liver, kidney, vasculature, skeletal muscles, pancreas, retina, adipose, neuronal, and reproductive tissue, have been shown to present local RAS [2–6]. Though systemic RAS can have a role in the regulation of cardiovascular homeo-

stasis, there is accumulating evidence to suggest that the local RAS may affect tissue angiogenesis, proliferation, cell growth, apoptosis, tissue inflammation, differentiation, hormonal secretion, fibrosis and/or dependent of systemic RAS. The local RAS has the paracrine effect in the tissue. Indeed, it does not have to come along with the systemic RAS [2, 5].

The liver is critical organ to maintain not only to glucose homeostasis [7] but also almost all of the body's metabolic activities. The liver tissue has a great regeneration capacity against to repair of liver injury also [8]. The organ has reported existing both of systemic and local RAS [7]. The chapter could, therefore, focus on the local RAS in liver. However, there are limited studies available to study on local RAS. So, the aim of the present chapter is to analyze and sum up the participation of local RAS on both physiology and pathophysiology of liver tissue.

2. The renin angiotensin system in liver

2.1. The component of local renin-angiotensin system in liver tissue

The component of local renin-angiotensin system in liver is divided two as a classical and alternative component of liver renin-angiotensin system.

2.1.1. The classical component of local renin-angiotensin system in liver tissue

Before starting to evaluate the physiological and pathophysiological importance of RAS, it should be given some recent findings about which component of RAS present in the liver tissue. Giving that the elements of the system are so important to bring out its effects on the target tissue, it is expressed that almost all of RAS components could present in the liver tissue, like other organ and tissue. One common consideration about RAS might be upregulation and/or disruptions of distributions of its components, including angiotensinogen, renin, ACE, Ang-II, and AT1 (**Figure 1**) [6]. One of the recent data shows that local RAS components were found at cholangiocytes [2]. Hepatic Kupffer cells [3] and nuclear region of hepatocytes [4] also locally produce angiotensin-II (Ang-II) [9].

Angiotensinogen, predominantly produced in the liver, is one of α2-globulin glycoproteins with 452 amino acids around 60 kDA [2]. Although angiotensinogen is well known to produce in the liver, local angiotensin synthesized was also reported in a few hepatocytes from and Kupffer cell in human tissue [8]. Although it is clear that the primary source of the precursor of angiotensinogen is the hepatocytes, Kupffer cells, and bile duct epithelium have produced to low level of angiotensinogen as well. Cirrhotic livers are reported to increase angiotensinogen and plasma renin level and activity in both humans and animal studies [6]. Depletion of angiotensin is emphasized to lead to hypotension, and kidney pathomorphological changes, decrease survival. The authors suggested that liver and brain angiotensin are enough to maintain blood pressure and prevent pathomorphological changes in the kidneys [10]. This information is emphasized that angiotensin produced from the liver is the primary source of the body.

Even though Ang-I production via renin has not been found in the liver tissue, some clues are indicated that *de novo* production of it might be found locally in hepatic-mesenteric vascular beds and circulation plasma as well [6].

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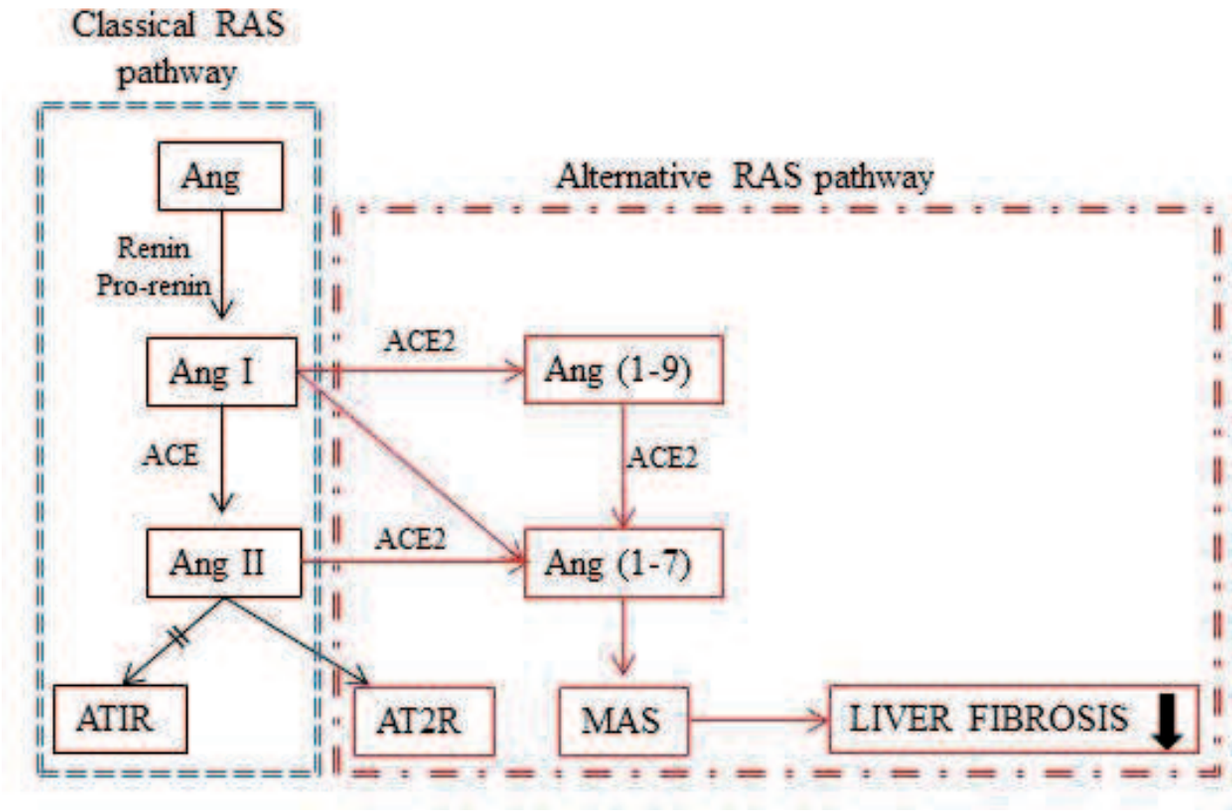

Figure 1. A schematic diagram of the classical and alternative renin-angiotensin system. ACE: angiotensin converting enzyme, ACE2: angiotensin-converting enzyme-2, Ang-I: angiotensin-II, Ang-II: angiotensin-II, Ang-1-7: angiotensin1-7, Ang-1-9: angiotensin1-9, AT1: angiotensin type-1receptor, AT2: angiotensin type-2 receptor, Mas: mas receptor. The figure was modified from Refs. [17, 18].

Renin is expressed at the liver as well [5–7]. It is surprising that renin expression in the female is higher than male in liver tissue of both mice and rats [7]. Furthermore, its expression was found at liver cells such as cholangiocytes, hepatocytes, and hepatic stellate cells (HSC) [9]. Renin receptor was reported to have low-level expression mRNA at liver and kidney, but the high level of the heart, brain, and placenta. Also, it was outlined that the animals have been reported to suffer from liver fibrosis, nephroangiosclerosis probably leads to the activation of ERK1/2 and enhancing of plasminogen activator inhibitor-1, cardiac, and aortic hypertrophy when prorenin transgene express at liver in the rats [11].

The expressions of ACE and AT1 are found at vascular endothelium, hepatocytes, and bile duct epithelial cells. This distribution could be changed under pathologic conditions. For example, in the fibrotic liver, fibrous septa, mesenchymal cells (HSCs and myofibroblasts), and Kupffer cells are also produced to ACE and AT1 [12]. AT1 is predominantly found in the liver. However, AT2 genes are found in a trace amount or not in the normal and pathologic liver as well. At the same time, it was reported so far that AT2 receptor gene expression was found from isolated human hepatocytes and stellate cells. This high expression of AT1 might be the elevation of the liver due to the participation of it in the inflammatory, proliferative process, and vascular effect in the liver. This info consists of fibrosis and the degree of portal hypertension to the AT1 expression on septal myofibroblast [6]. The receptor is pointed out to

be at hepatocytes, HSCs, Kupffer cells, bile duct cells, myofibroblast, and vascular endothelial cells [12]. One of the previous studies is stated that ACE could present only liver at tissue-specific ACE knockdown animals, but not a gastrointestinal tract, heart, vascular or spleen. The only kidney might be seen ACE activity but at a trace level. Additionally hepatocytes, the testis is also found express of ACE at liver-specific ACE knockdown mice. Although there is no ACE found at vascular, blood pressure at liver-specific ACE knockdown mice is reported to be pretty standard. The authors implied that adequate ACE in the liver controls the essential kidney function for maintaining homeostasis, but there is no obligation to present of vascular ACE expression to regulate normal blood pressure. Indeed, adequate ACE in any organ is enough to maintain kidney function, resulting in mean blood pressure control [13].

Ang-II might be present in cholangiocytes and activated HSC which is also highly express active renin, ACE at *in vitro* and *in vivo* studies [14]. Some recent studies have been shown that AT1 could present in the liver [5]. Ang-II production from cholangiocytes probably increases at bile duct ligation (BDL). The expression of RAS component at different liver cell types might have both paracrine and autocrine impact on the target tissue. It seems that activation of cholangiocytes RAS could trigger the other cell type's RAS. This concept may help us to explain how to relate RAS at liver pathologies [14]. Many RAS components, such as renin, ACE, Ang-II, AT1, and ACE2 seem to be un-regulated under pathophysiological conditions [7]. But, Ang-II that can exist in the liver tissue could enhance at the pathophysiologic circumstance [6]. Ang-II relates to promoting some liver disease, i.e., liver fibrosis, and proliferation and activation of hepatic stellate cells. So, there is reported to have some prophylactic effects against to liver failure [7]. One of the previous studies noticed that active RAS blocking by either angiotensin-converting enzyme (ACE) or AT1 inhibition led to attenuate liver fibrosis by suppressing HCS and hepatic TGF-β1 in chronic liver injury [9]. The component of local RAS was found in the liver of obese and type-2 diabetes patients. The upregulation of angiotensinogen in liver was shown in type-2 diabetic patient with and without obesity. Its upregulation expression was also determined at hyperglycemia in obese Sprague-Dawley rats, but not in nondiabetic and diet-induce obese rats. Therefore, it is likely to diabetes than obesity much more related to hepatic angiotensinogen production. There is an active interaction determined between TNF-α and local RAS in liver. So, TNF-α increases ACE, angiotensinogen, and the expression of angiotensin AT1 mRNA in the liver. At this moment, the upregulation of local RAS may in the liver is associated with obesity and developing insulin resistance and liver fibrosis [14].

Recent studies have shown to the paradigm shift of RAS. Ang-II receptors and some proteins have been proved to interact with each other by using several methods. For example, it has been indicated that AT1-related protein probably acts a negative regulator, including its cell proliferation and vascular remodeling by enhancing AT1 internalization. Angiotensin type-2 receptor (AT2)-related protein has an adverse impact on the AT2 effect, e.g., growth. Furthermore, AT1 might form either homodimers or heterodimers with other partners, including AT2, bradykinin B2 receptor, epidermal growth factor (EGF) receptor, dopamine receptor, endothelin receptor type B and Mas receptor. This dimerization of Ang-II receptors is unknown neither physiologic nor pathophysiologic importance. Therefore, more new studies are needed to get a better understanding of the dimerization function under physiologic and pathophysiologic

conditions [15]. Also, there is indicated to be the active interaction between RAS components in the mammals. The interaction was shown when renin or Ang-II infusion at perfused mammalian liver enhances angiotensinogen release, and this effect does not link the glucocorticoid secretion. But glucocorticoid present is required to maintain angiotensinogen gene synthesis. It should not rule out that such a kind of studies were carried out by using at the supraphysiologic level of Ang-II. But, it also pointed out this positive interaction could be a more pathophysiologic circumstance, such as depletion of sodium and water and hemorrhage, too [16].

2.1.2. The alternative component of local renin-angiotensin system in liver tissue

Alternative pathway has been thought for a while (**Figure 1**). The alternative paths are ACE2 and chymase that are discuss in this chapter. ACE2 is found at heart, kidney, gastrointestinal tract as well as liver and lung. ACE2 is one of the type-I integral proteins, expressed fundamentally at the cell surface as an ectoenzyme. ACE2 has ectodomain at the membrane; however, metalloprotease ADAM17 is reported to modify to make an active soluble form of it. So, its soluble form could be detected in plasma and urine as well. Moreover, ACE2 is one of the members of the M2 zinc metalloproteinase family as well as somatic and testicular types of ACE. ACE2 has 805 amino acid residues and similarities with human ACE at 41%. Although somatic ACE has two active sites at N- and C-domains, ACE2 has only one active site. The other difference of ACE2 from ACE is a carboxypeptidase, but ACE is a peptidyl dipeptide. Moreover, ACE2 is reported not to blockage by using any ACEI, e.g., captopril, enalaprilat or lisinopril. ACE2 can cleave only one residue from C-terminus of Ang-I and Ang-II that have limited biological effects. The ACE2 effects on Ang-I and Ang-II could produce angiotensin-1-7 (Ang-1-7) and angiotensin-1-9 (Ang-1-9), respectively. But, in these two pathways Ang-1-7 is produced more likely by ACE2. That is why ACE2 could accept to provide Ang-1-7. Ang-1-7 interacts with AT2, BK2 and Mas receptors. Taking together this finding, ACE2-Ang-1-7-Mas axis could modulate the axis of ACE-Ang-II-AT1 [6]. Based on these findings, it is reported that Mas-binding Ang-1-7 produced by ACE2 is the fifth receptor of RAS. ACE2 was increased in liver injury and cirrhosis, resulting in enhancing Ang-1-7 at the plasma and tissue level. The local RAS elements are introduced to express from the cancerous tissue. Some evidence has been shown that RAS is related liver cancer. For example, ACE and AT1 antagonist drugs (captopril, irbesartan; respectively) give rise to minimize cancer growth, liver metastases and angiogenesis in colorectal cancer liver metastases animals [5]. It was shown that ACE, Ang-II and AT1, classic components of RAS, were high expression in rats with biliary fibrosis as well as ACE2 in liver, and plasma, Mas in liver, Ang-1-7 in plasma. This finding can be concluded that local RAS in the liver has both classical (ACE-Ang-II-AT1) and ACE2-Ang-1-7-Mas pathways that play important role in chronic injury. RAS pharmacologically inhibition by ACE and AT1 inhibitors is well established to have a therapeutic effect on many diseases including hypertension, heart failure or diabetes due to blocking Ang-II and AT1. Some recent evidence has been pointing out that these inhibitions have caused to elevate ACE2 and Ang-1-7. The most impressive result from these kinds of experiments is that there is no functional effect of ACE2 elevation in normal animals. Therefore, ACE2 elevation could conclude to be pivotal importance under the only pathophysiologic circumstance, but not a physiologic condition [6].

The other alternative Ang-II production process is via chymase. The enzyme, chymase, is a chymotrypsin-like, presents in the mast cell secretory granules. It is also produced as an inactive form and activated by dipeptidyl peptidase I (DPPI), a thiol proteinase, in the mast cell granules. The optimal pH for DPPI is at 6.0. But mast secretory granules have controlled at 5.5, and there is no chymase activity at 5.5. The optimal pH for chymase is around 7 and 9. As soon as the chymase is secreted into interstitial tissue at 7.4, it can reach to its optimal pH, resulting in gaining activation. The only mast cell-stimulated tissue can secrete it under inflammation circumstance because there may be found any chymase inhibitors in the regular target. Chymase can produce Ang-II from Ang-I. Additionally, chymase can activate TGF-β and metalloproteinase-9 (MMP-9) from their inactive forms. Both of them participate in tissue fibrosis and inflammation. It is stated that there might be a positive correlation between Ang-II and chymase in the human liver fibrosis due to finding a high level of both. Moreover, it is suggested that chymase and Ang-II levels could indicate fibrotic severity. So, chymase inhibition could alleviate the liver fibrosis in animal models. Therefore, new studies are required to clarify the interaction of chymase, Ang-II, and liver fibrosis [19].

2.2. Intracellular pathway of local renin-angiotensin system in liver

Ang-II is reported to cooperate with an intracellular signal pathway to amplify its effect. Therefore, in this section some recent information about the intracellular mediators of local RAS is given. One of these signal amplification pathways may be mitogen-activated protein kinases (MAPK), which are ERK1/2, JNK, and P38 MAPK. MAPK plays a crucial role in cellular differentiation, proliferation, migration, and fibrosis. ERK1/2 has some vital effects on cholangiocyte proliferation. Additionally, MAPK, Ang-II can activate nuclear factor-κB (NF-κB) [20]. Ang-II gives rise to trigger proliferation by stimulation of the cAMP signal pathway [9] as well. It is noticed that human fibrotic liver samples were found less AT1 expressing at hepatocytes, but high expressing in hepatic stellate cells (HSCs), vascular endothelium, and bile duct epithelium. The local RAS-induced HSC via AT1 and activation of NADPH oxidase results in fibrotic liver, and cholangiocyte proliferation by AT1 triggering a cAMP, PKA, ERK1/2, and pCREB-dependent signaling pathway [9]. Hepatic stellate cell (HSC) is the most effective cell type of liver to the deposit of connective tissue at respond of liver injury. Fifteen percentage of liver tissue composes of HSC. Both of Ang-II and renin are reported to increase liver cirrhosis patients. It is reported that Ang-II might relate to the development of the liver fibrosis by activation of HSC via TGF-β1 through AT1. This exacerbating effect of Ang-II on liver fibrosis probably mediates phosphorylation of c-Jun and p42/44 MAPK in AT1. Activated HCS produces Ang-II that led to fibrosis via NADPH oxidase. Also, a definite link is found between TGF-β1 and Ang-II for the development of liver fibrosis. Therefore, Ang-II may give rise to elevated TGF-β1, resulting in the production of collogen-1 via AT1 in the liver. There is a kind of positive feedback in the liver which is that TGF-β1 activates HSC, and HSC can produce much more TGF-β1 production [21].

Most of these injury factors are linked to oxidative stress based on reactive oxygen (ROS) and reactive nitrogen species. The ROS production is produced by some enzymes, for instance, mitochondrial leakage, tetrahydrobiopterin coenzyme oxidation, xanthine oxidase, endothelial nitric oxide synthase, nicotine adenine dinucleotide phosphate (NADPH) at both

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membrane and cytosolic compartment [2]. It might seem that oxidative stress is also critical pathways for RAS's effect, especially in development of pathologies [22]. HSC could also relate to oxidative stress by increasing AT1 and nonphagocytic NADPH oxidase enzyme system. NADPH oxidase is one of multicomponent enzyme systems, which is activated by rac1, p47phox, gp91phox, p22phox, nox1, p40phox, and p67phox. Ang-II triggers p47phox phosphorylation via AT1 on activated HSC to increase ROS production. One of the AT1 receptor antagonists, losartan, could block the ROS formation through NADPH oxidase inhibition [23]. This formed superoxide by NADPH oxidase could oxidize tetrahydrobiopterin (BH4) that is a cofactor of nitric oxide synthase (NOS). So, if BH4 is formed at high concentration, NOS enzyme could be dimerized and produces nitric oxide (NO). But, when the BH4 level is low, the balance between NOS and BH4 can shift to produce superoxide, resulting in decreasing NO production but increasing peroxynitrite (ONOO) formation. So, AT1-initiated oxidative stress could lead to inactivate NO, lipid oxidation, and activate redox-sensitive genes, e.g., proinflammatory cytokines, matrix metalloproteinases, chemotaxis, and adhesion molecules [15]. So, local RAS can produce ROS via Ang-II-AT1 axis [2].

Ang-II might relate to inducing tumor progress interaction with HSC in liver. Ang-II activates cAMP but not IP3. But many studies have shown that AT1 activates IP3, diacylglycerol, and reactive oxygen species. The activation of cAMP by Ang-II was also shown in renal mesangial cells. Moreover, PKA/ERK/CREB signaling pathway is reported to be an important intracellular component of the Ang-II effect on stimulated biliary proliferation. This notion was supported by attenuation of proliferation through inhibition PKA and ERK1/2. This intracellular pathway was present cholangiocytes that have shown own local RAS. Ang-II causes fibrosis by expresses of collagen 1A1 and fibronectin 1 in a primary rat cholangiocyte cell line, as well as IL6, which is one of the proliferative cytokines playing a role in biliary hyperplasia [9].

The other pathway might be Jak2/STAT for local RAS in the liver. Jak2 kinases are vital for the transcription of angiotensinogen mRNA *in vivo*. Ang-II stimulates STAT5B and coactivator of it, p300, in the liver. It is also stated that STAT3/p300/CBP pathway is critical for IL6 dependent activation of human angiotensinogen gene in HepG2 cells. NF-κB might involve Ang-II's inflammatory response, as well as IL-6, inducing the hepatic acute-phase reaction [24].

Ang-II has played an important role in the development of fibrosis, including liver, heart, lung, and pancreas. Some soluble factors such as cytokines, oxidative stress, chemokines, and growth factor increase ECM production [25]. TGF-β1 is one of the most profibrotic cytokines to accumulate some extracellular matrix (ECM) [15]. Local Ang-II predominantly induces of TGF-β [25]. Some of ECM element is noncollagenous glycoproteins, including hyaluronic acid (HA) and proteoglycan. Therefore, elevation of HA in plasma is given an important clue to assess the diagnosis of liver fibrosis. Ang-II is locally synthesized by activated HSC, moreover, and crucially involves the development of liver fibrosis. α-SMA is considered to be an important indicator for activation of HSC. It is reported that the positive effect of Ang-II is not only to activate and/or proliferate of HSC but also elevate fibrogenic cytokine, collagen deposition, and matrix synthesis. When RAS can block by using inhibitors for AT1 or ACE, Ang-II's fibrotic effects decrease. Local RAS plays a crucial role in the development of liver fibrosis

[15]. How local Ang-II can help established the fibrosis may be related to transforming growth factor-beta (TGF-β). More attention would give for the interaction of Ang-II and TGF-β. There are many TGF-β isoforms; however, TGF-β1 is the most investigated isoform. TGF-β associates the intracellular Smad signaling. Therefore, the TGF-β/Smad signaling is reported to play a crucial role to accumulate collagen, one of the major component proteins of the extracellular matrix (ECM), resulting in tissue fibrogenesis. Smad acts the most important transcriptional factor for TGF-β-mediated responses including fibrosis. Ang-II has been indicated to induce Smad2 and Smad4 signaling via AT1 for gene transcription, but the transcription is not strictly bound to TGF-β. Also, Smad7 has a function to counteract of the TGF-β pathway. Moreover, when Smad3 is decreased, or Smad7 expression is increased, tissue fibrosis from liver, skin, or kidney is indicated to diminish. Downregulation of CTGF is also prevented from developing fibrosis. CTGF is one of the crucial elements of fibrosis at a couple of organs. CTFG is a potent trigger of myofibroblasts and ECM synthesis and deposition. So, CTFG is upregulated by Ang-II by AT1, resulting in activation of Smad signaling and independent Rho/Rho kinase pathways of TGF-β. Based on these findings, both ACE and AT1 antagonists could alleviate CTGF expression and fibrosis as well. Also, the reverse can do the same effect on fibrosis [25]. Not only does TGF-β decrease the degradation of the matrix by metalloproteinase (MMP) but also synthesize connective tissue growth factor (CTGF), which is autoinduction of TGF-β. That is why Ang-II blockage by ACE or its receptor inhibition could reversed the tissue fibrogenesis in target tissue by modulation of TGF-β1 expression. Fibrosis is one of chronic and progressive processes mediated by the complex interaction between cell, ECM, cytokine, and growth factor. However, there is still no efficient and well-tolerated antifibrotic therapy due to lack of the main molecular pathways of it. The inhibition of Ang-II is reported to attenuate 40–60% TGF-β1 production, resulting in a reduction of hepatic fibrosis. Ang-II can stimulate Smad pathway also activate CTGF by TGF-β independently. The interaction of local Ang-II and TGF-β1 should, therefore, be elucidated in previous studies [25].

2.3. The function of local renin-angiotensin systems in the liver tissue

Locally formed angiotensin peptides have aggravated system's effects, notably cell growth, antiproliferation, apoptosis, production of reactive oxygen species (ROS), secretion of the hormone, proinflammatory and profibrogenesis. Till date, the importance of hepatic RAS under both physiologic and pathophysiologic condition has not been evaluated well yet, expect for heart and kidney [6]. However, the local RAS becomes so important to under pathophysiologic conditions in hepatic tissue based on the little present of RAS members compared to systemic RAS [12]. The local RAS plays a paracrine role in modulation of some processes, including inflammation, fibrosis, angiogenesis, cell proliferation, apoptosis, and survival under both physiological and pathophysiological circumstances. After recognition of an alternative RAS pathway (ACE2, Ang-1-7, etc.), it has to be changed to view its importance of tissue function. The task can be divided as its action on the systemic level including blood pressure control, tissue perfusion, and sodium and fluid balance, and on paracrine level including proliferation, inflammation, angiogenesis, apoptosis [17]. Consequently, local RAS might be amply of some diseases at liver since angiotensin-II gives rise to trigger oxidative stress. Moreover, the liver has an important role to detox of toxin which means that

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it may be very susceptibility to oxidative stress [22]. Recent data, from animal and human studies, suggest that the counteraction of local RAS would be of importance in modulating of liver diseases. The RAS not only can regulate blood pressure and volume, but also modulates inflammatory process [20]. The local RAS has importance under both physiologic and pathophysiologic conditions [6].

Local RAS plays a pivotal role for the tissue function both physiologic and pathophysiologic conditions based on paracrine and autocrine impacts of it [26]. RAS also modulate the body metabolic process [18]. Locally produced RAS has some specific role in apoptosis, angiogenesis and regulation of cell proliferation [27]. The RAS is thought to participate probably in liver regeneration and tumor as well [27]. Ang-II is important because of its effects including vasodilatation, antiproliferation, elevation of baroreflex sensitivity, facilitation of bradykinin activity at bradykinin receptor (BK2), inhibition of C-domain ACE activity and AT1 receptor antagonism, but some of them are counteract with Ang-II effects [6]. It is necessary to find the answer of the question why the local RAS has crucial regulation of tissues. One of the explanations of the issue is that the amount of local RAS components is independently controlled by its level in tissue [28]. It means that the mimetic or antagonist drugs could not be able to alter of the RAS members' concentration. The other possible explanation of it is that local Ang-II has a vital role in controlling of sympathetic neurotransmission and smooth muscle hyperplasia without effects of sodium balance which is under controlled by systemic Ang-II [28].

RAS was probably reported to be related to some hepatic pathogenesis, including hepatic stellate cell inflammation, proliferation, elevation of portal vein pressure, and hepatic fibrogenesis, as well [29]. RAS activation was reported in the patients with liver cirrhosis [30, 31], liver inflammation [12], nonalcoholic fatty liver disease [12], and fibrosis [4, 9]. RAS triggers oxidative stress at liver [32]. Moreover, blockage of RAS in the liver has improved for regeneration and inhibition of tumor progression [17]. There is an active interaction between the plasma ACE level and patient with liver fibrosis [29]. On the other hand, the local production of Ang-II might not be entirely blocked by ACE inhibitors due to that there are alternative pathways that are chymase [33].

Angiotensin-II, the most active member of RAS, has been indicated to have some pathologic effects, such as inflammation, oxidative stress, prothrombotic [18], cirrhosis [34], and acute liver injury [35]. Ang-II causes to contract vascular smooth cell and triggers nicotinamide adenine dinucleotide phosphate oxidase (NADPH), thereby elevation of superoxide radicals [20]. Interestingly, local RAS in liver and tumor necrosis factor-alpha (TNF-α) was suggested to have some interaction for developing insulin resistance and atherosclerosis by activation of plasminogen activator inhibitor-1 (PAI-1) production [14]. By better knowledge of inhibition, local RAS in the liver might be able to prevent at least of these kinds of diseases. Local RAS has a pivotal role under the pathophysiologic circumstance, resulting from tissue inflammation, trauma, hypoxia-ischemia, ischemia-reperfusion, hyperglycemia, hyperlipidemia, hyperhomocysteinemia, and hyperuricemia and autocrine/paracrine effect on the target organ [2]. One of the recent studies reported that RAS blockage by using ACE, captopril, inhibits the liver tumor growth in mice. Moreover, captopril was indicated to increase liver regeneration as well. How the captopril could enhance its recovery might be explained by increasing of HCS.

HCS can secrete MMP-9, resulting in accumulation of extracellular matrix. HCS could produce some terminating factors including IL-1, TGF-β at the late stages of liver regeneration [27].

In addition to other effects, Ang-II could modulate the immune system by releasing macrophage/monocyte chemoattractant protein (MCP)-1, MCP-2, granulocyte colony-stimulating factor as well as increasing macrophage infiltration. It might be thought that macrophage infiltration can fight microorganism and tumor cells. The macrophage's role in the late stage of tumor development is still needed to clarify. But some evidence is shown that macrophage infiltration might trigger cancer growth and metastasis. For instance, Kupffer cells could promote immune escape and facilitate metastatic colonies at a late stage of the disease. The macrophages could produce many cytokines to initiate angiogenesis, tumor growth, and metastasis. It is reported that Ang-II could stimulate macrophage infiltration and angiogenesis through AT1 and VEGF in a melanoma model. There might be an active interaction between macrophage and Ang-II. Because macrophage could produce ACE for the synthesis of Ang-II [5]. Ang-II increases the production of TNF, IL-1β the infiltration of CD43+ inflammatory cells which are inflammatory proteins [36].

2.4. The crosstalk of local renin-angiotensin system and liver pathologies

This chapter's main aim is underlined of local RAS and its contribution of liver pathologies. But, it should be accepted that there is a limited study to evaluate or investigate this interaction. Analyzing the interaction might be difficult. Because local and systemic RAS are hard to distinguish from each other. Also, they both could involve in developing liver pathologies or changing of liver function for some cases. That is why it will be divided the subhead of each liver pathology.

There are many factors determined to cause to liver diseases, such as alcohol, viral hepatitis, drug abuse, and autoimmune hepatitis. Chronic damage to liver causes liver fibrosis, leading to liver cirrhosis. Liver fibrosis is also produced by type-2 diabetes, concerned with obesity and steatosis that is fat accumulating in the liver [18]. There are two main cell types to overcome that kind of pathologies, as well as healthy maintaining the liver function. One of these cells is Kupffer cells. The cells are a type of mobile macrophages bound to endothelial cells. The cells physiologically synthesize immune-suppressive cytokine such as IL-10 to block HSC activation and/or collagen production. When the liver is injured, Kupffer cells are activated and start to release inflammatory cytokines, associating with apoptosis. But, the others such as IL6 or IL-1ß could involve liver fibrosis by increasing ECM, collagen-I, some fibrogenic cytokines such as TGF-ß1. The second type of cells is hepatic stellate (HSC), perivascular mesenchymal cells that are located in Disse space at the liver. The task of HCS is to metabolize vitamin-A, synthesize cytokines, growth, and inflammatory factors. That is why the cell plays a vital role in development of liver fibrosis and also participate liver inflammation [18]. High activation of ACE and angiotensin-II type-1 (AT1) receptor suggests at the liver disease. Furthermore, AT1 at liver plays a role in HSC activation by phosphorylation of Janus kinase-2 [37]. Besides, AT1 knockout mice were shown to decrease hepatic fibrosis. Also, Ang-II stimulates to the hepatic stellate cell for production more Ang-II [32]. When Kupffer cells are triggered by oxidative stress to produce proinflammatory cytokine after liver degenerations, resulting in also activation of HSC subsequently to synthesize collagen. After activation of

HSC, the cells moves to the degenerative area, then transform into interstitial myofibroblast. The myofibroblast can also produce cytokines, chemokines, matrix metalloproteinases, and tissue inhibitors of metalloproteinase (TIMPs). Local Ang-II has also affected on endothelial function. The endothelial cells have many tasks for regulation vascular tone, coagulation, cell growth, and leukocytes migration. All of the function of the endothelial cell requires a balance between vasodilatation such as nitric oxide and vasoconstriction such as Ang-II. Endothelial cell is very sensitive to the cell redox state [18].

2.4.1. The local renin-angiotensin system in liver and portal hypertension

Portal hypertension is one of the complications of cirrhosis having high of morbidity and mortality rates. Portal hypertension is interacted with RAS and sympathetic system, resulting in retention of water and salt then ascites [38]. If portal hypertension could be decreased, the complications of it could be declined as well. One of the drugs causing to reduce portal pressure is RAS inhibitors. Based on the suggestion, cirrhosis might cause vasodilation at the systemic and splanchnic vessel, so RAS could be activated to make up for the hypotension, resulting from Ang-II production. Elevated Ang-II gives rise to high-intrahepatic resistance both static and dynamic ways, and portal venous inflow through sodium and water retention. Ang-II also increases aldosterone production which has been thought to participate in developing inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and fibrosis. But, there is still more evaluation for analyzing of the beneficial effect of RAS inhibitions on the patient with portal hypertension-induced by cirrhosis. Not only does Ang-II cause vasoconstriction in the hepatic microvasculature, but also endothelin, thromboxane-A2, leukotrienes, and norepinephrine also cause the vasocontraction. Therefore, it might be suggested that nitric oxide (NO) could not have efficient enough to overcome of that vasoconstriction. NO impairment could, therefore, help to progressive of liver dysfunction. So, the blockage of RAS may have a therapeutic effect on the early stage of cirrhosis. The local RAS might have some contributions to developing portal hypertension and virtually cirrhosis [39].

2.4.2. The local renin-angiotensin system in liver and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) has been reported to be the most prevalent type of cancer throughout worldwide [30], being the fifth most predominant tumor case [17]. The patient with HCC has been informed to have only 5 years survival due to metastasis and recurrence based on angiogenesis [30]. HCC is one of the most severe complications of cirrhosis [6]. Although liver is one of the few tissues having regeneration, liver resection can perform at HCC and colorectal cancer (CRC) liver metastases patients for removing tumorous part of tissue [17]. CRC is the second leading cause of death at both genders, most of which are related to liver metastasis by 70% of CRC patients [17]. Liver resection is maybe best treatment for these diseases [17]. Also, some patients are indicated to die after liver resection operation due to metastasis of liver from the inside or outside tissue. This tumor recurrence is suggested based on some factor elevation including growth, angiogenic factor, and also modulation of extracellular matrix [17].

It is speculated that RAS might participate in liver regeneration and tumor modification by tumor proliferation and apoptosis, angiogenesis, and ECM remodeling [17]. RAS might

participate in the development of this carcinoma due to its angiogenic and proliferative effects. Moreover, Ang-II could enhance vascular endothelial growth factor (VEGF), the most efficient angiogenic factor, which is decline by ACEI in mice with tumor [6]. Therefore, studies are indicated to be interaction Ang-II and vessel cancer growth. ACE having a homolog of ACE can convert to Ang-1-9 and Ang-1-7 from Ang-I and Ang-II, respectively. Elevated ACE2 is reported to block cell invasion, angiogenesis, VEGF in non-small cell cancer cell line. The activation of VEGF by Ang-II is thought to be concerned with VEGF/eNOS pathway and inflammation as well. So, it is well documented that RAS plays a role in cancer progression or metastasis. Moreover, the alternation of RAS element in the local cancer tissue might be related to cancer severity. RAS could be elevated in the patient with cirrhosis, found a high level of both Ang-II and Ang-1-7. Ang-1-7 is a potent antifibrosis. Ang-II can trigger VEGF in dose and time-dependent manner, also HSC for contraction and proliferation. One of the studies was shown that AT1 inhibition markedly declines liver fibrosis and VEGF expression. So, they pointed out that the interaction of Ang-II-VEGF is so important for the development of liver fibrosis and HCS activation. HCC patients were shown to have low expression of ACE2, although Ang-II, ang-1-7 and VEGF were high levels in the patient [30].

In addition to VEGF, Ang-II's angiogenic effect might be concerned with epidermal growth factor, angiopoietin 2, basic fibroblast growth factor, and an insulin-like growth factor that plays a major role in both liver regeneration and tumor growth. Moreover, both systems are reported to associate with liver regeneration. Although ACE-Ang-II-AT1 axis might be enhanced at early stages of its restoration, ACE2-Ang-1-7-Mas axis could be activated at the later stages of the recovery. RAS expression was reported to be cancer specific alternation. For examples, CRC metastases were indicated to elevate AT2, ACE, and Mas expressions, but decrease AT1 and angiotensinogen expressions. Moreover, AT1 was speculated to be healthy tissue cells, including Kupffer as well as the tumor and stromal infiltrating cell. But, the other RAS receptors, e.g., Mas, were found an only tumorous liver tissue. The other example was indicated that ACE localization was suggested to be hepatic endothelial cells, apical and cytoplasm of cancer and vascular cell because of neovascularization and cancer cell homeostasis. Also the other CRC metastases from colorectal adenoma, sarcomas prostate cancer was also speculated to be the crucial importance of RAS. So, pharmacological blockage of RAS by ACE or AT1 antagonist gives rise to decline the growth of cancer. ACE antagonist was probably decreased the severity of tumors in some kinds of tumor, e.g., prostate, breast, and CRC. The other view was pointed out that cancer growth could be a decline in AT1 knockdown mice based on attenuation of VEGF, angiogenesis. This finding was suggested that AT1 plays an important role. Also, the drop of AT1 might cause to enhance alternative RAS pathway action (ACE2, Mas). The other explanation of these was that when AT1 was chronically blockaded by the drug, it might be shifted a balance to AT2 which is well known to have a different effect from AT1. Although AT1 has mitogenic and angiogenic effects, AT2 triggers apoptosis and inhibits proliferation. AT2's effect on VEGF is the double direction. AT2 is reported to activate VEGF; it is also shown to antagonize VEGF as well. The other aspect should also be considered that AT2 could modulate NO and BK pathways in which both has participated angiogenesis. Moreover, the other candidate for

angiogenesis process could be proliferator-activated receptor-γ (PPAR-γ) because plenty of AT1 antagonists enhanced PPAR-γ attenuation of cancer proliferation. Why many of studies have focused on the regulation of angiogenesis by RAS is related to how to regulate tumor growth. But it should be noticed that Ang-II could be produced by another enzyme, chymase which also enhance Ang-1-7. Thus, ACE inhibitors can just block one way, resulting in one alternative pathway still efficient for its production. The other important point is that the alternative RAS pathway could syntheses Ang-1-7as well. Ang-1-7 has been reported to reduce metastases in mice since it led to diminish in cyclooxygenase-2. Elevation of cyclooxygenase-2 is related to cancer growth, inflammation, angiogenesis, thanks to enhancing prostaglandin E2, D2, and thromboxane A2. Ang-1-7 could also moderate thromboxane A2 as well as prostaglandins. ACE inhibition increases not only Ang-1-7 levels but also BK levels. However, the elevation of BK is not beneficial effect on the tumorous cell due to stimulation of cancer growth by angiogenesis and inflammation [17].

2.4.3. The local renin-angiotensin system in liver and cholangiocarcinoma

Cholangiocarcinoma (CCA) is one of the uncommon malignant tumors. This tumor type is also related to local RAS. According to a recent study, the development of CCA is associated with inflammation and biliary duct cell injury due to obstruction of bile flow rate. Cytokines productions in the biliary tissue by inflammation process are responsible for the malignant transformation. Locally produced Ang-II is reported to involve to the proliferation and activation of CCA cells which express Ang-I as a growth factor in local effect (autocrine and paracrine). The local effect of Ang-II could modulate the balance between intrahepatic proliferation and fibrosis. Moreover, the patient with CCA was found to high ACE level. That is why it will be vital to understand the interaction of CCA and RAS in developing new strategies for cancer therapy to improve the patient's life and life quality as well [40].

2.4.4. The local renin-angiotensin system in liver and cancer growth

Cancer growth and metastasis are well documented to related angiogenesis. The new vessel growth is associated with Ang-II and VEGF/VEGF-A, especially useful in vascular endothelial cells. Ang-II's new vessel formative effect is through AT1. Its angiogenic effect of Ang-II is consisted within several cancer models. For instance, VEGF is shown to secrete through Ang-II-AT1 in ovarian cancer cells. Also, ACE inhibitors are reported to decline the neovasculature in cancer tissue. VEGF is defined to use similar pathways in many tissues. After VEGF overexpression in cancerous tissue, the fibrin at extravascular is accumulated, but the extracellular matrix is degraded. Then, the endothelial cell can migrate into the stroma, forming enlarged but thinned vessel-walled, named as mother vessel. After this stage, the vascular development is reported to differ from each tissue and many daughter vessels from mother vessel could be developed branches and caused to disrupt vessel organization, including muscular arteries and veins and produced glomeruli bodies, a kind of disorganized tangle vessel (**Figure 2**). Ang-II is indicated to enhance vascular permeability by increasing some permeability factors such as prostaglandins, nitric oxide, NF-κB, VEGF, and endothelin [5].

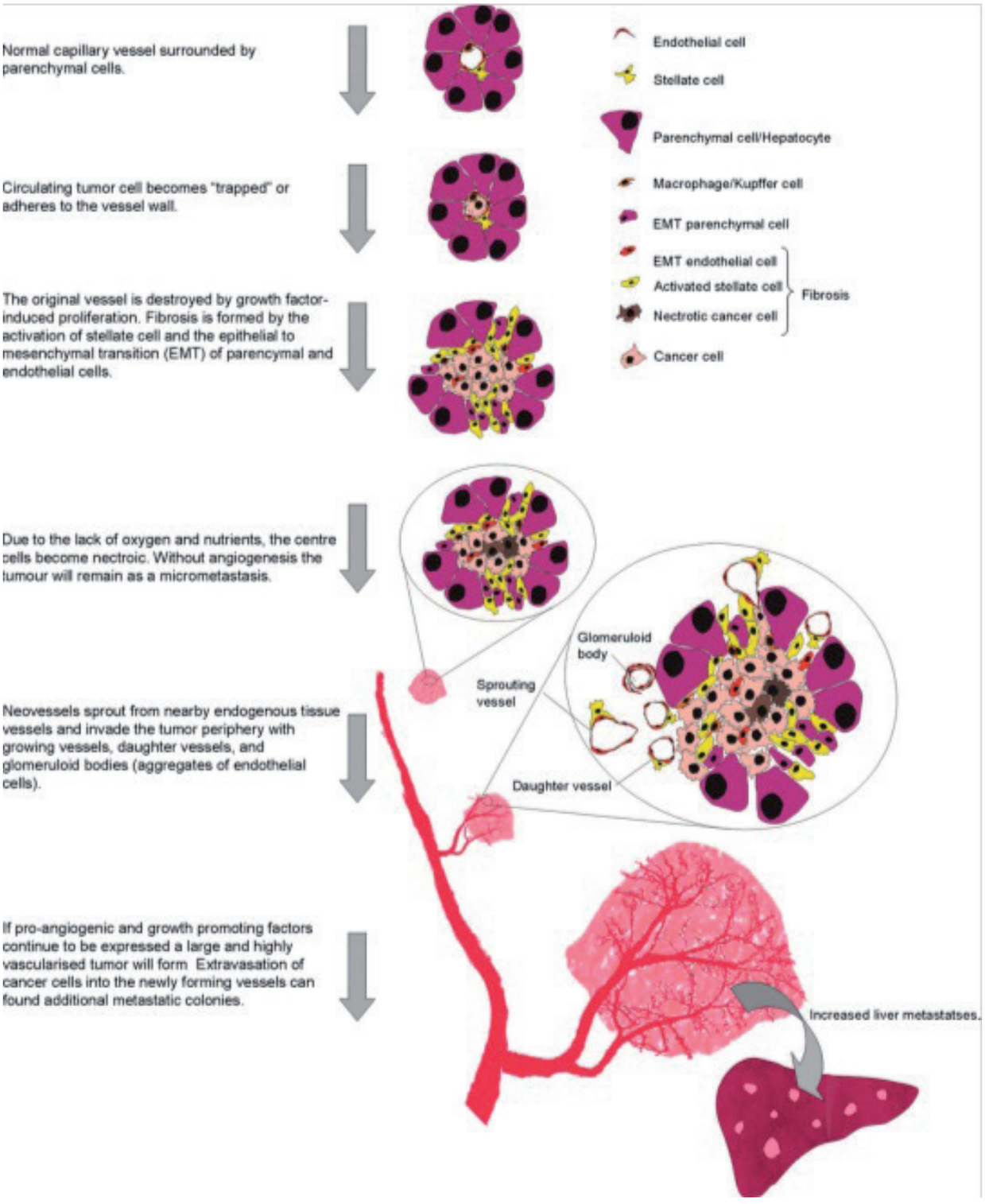

Figure 2. The development of cancer angiogenesis, growth and metastasis [5].

2.4.5. The local renin-angiotensin system in liver and cholangiopathy

Primary sclerosing cholangitis (PCS), an ischemic cholangiopathy, might be related to local RAS within the portal tract. Ang-II production may increase in portal tract due to biliary epithelial stimuli, including infections, drugs, and toxins. The other possibility of activation of RAS in it-portal tract relies on localized biliary tract ischemia such as microvascular

thrombosis; immune-mediated endothelial is or toxic injury to arterioles. Local RAS in the liver has suggested that Ang-II could modify bile secretion by elevation of the production of bile acid independent bile flow and by the nonvascular effect of Ang-II on hepatocytes or biliary epithelial. Elevation of Ang-II production can trigger some responses, such as inflammatory cytokines releasing from mesenchymal cells, biliary epithelia, and vascular endothelial, inflammatory cells influx, and the activation of portal tract mesenchymal cells with fibrogenesis. There is a vicious cycle with lymphocytic obliteration and occlusion of the peribiliary plexus and hepatic artery microvasculature, and biliary tract ischemia. These alternations give rise to enhance portal tract edema and venous pressure, promote cholestasis as well [41].

2.4.6. The local renin-angiotensin system in liver and insulin resistance

The liver is well known to regulate blood glucose that is why insulin could block glucose production on hepatocytes and indirectly decreasing lipolysis in the adipose tissue, and free fatty acids. When insulin resistance is developed it enhances gluconeogenesis and lipolysis to elevate glucose and free fatty acids in circulation. Therefore, liver tissue plays pivotal role in developing insulin resistance [2]. Metabolic syndrome, in other words insulin resistance [12], is a complex disease related to obesity, dyslipidemia, hyperglycemia, and hypertension as well. Metabolic syndrome is one of the risk factors for developing type-2 diabetes and cardiovascular diseases [42]. Therefore, this kind of illness might also be related to insulin resistance.

Ang-II involves the development of the insulin resistance [15]. Ang-II declines the insulin-stimulated tyrosine phosphorylation and thus to block the interaction between phosphatidylinositol-3-kinase and insulin receptor substrate (IRS-1) and downregulation insulin receptor signal. Hence, Ang-II increases liver glycogenolysis and thus increases gluconeogenesis. Taking together, these findings indicated that Ang-II could impair insulin metabolic effects, thus participating in developing insulin resistance. Also, Ang-II led not only to decrease lipid storage capacity and triglyceride at adipose tissue but also increase the accumulation of triglyceride in liver tissue. These effects might have a well-established pivotal contributing to developing insulin resistance as well. So, ACE inhibition is reported to improve the insulin sensitivity [43].

The local RAS in the liver might link to improve the insulin resistance related to plasminogen activator inhibitor (PAI)-1 in liver tissue. Furthermore, PAI-1 might be activated by TGF-β. Takeshita et al. also found that TNF-α increased PAI-1 both mRNA and protein productions in hepatocytes. They reported of TNF-α could trigger the protein kinase C (PKC), p38 mitogen-activated protein, kinase/extracellular signal-regulated kinase (ERK), protein tyrosine kinase, and NF-κB pathways to induce PAI-1 production in the liver. Ang-II activates PKC and NF-κB by 1,2-diacylglycerol production in primary rat hepatocytes. At this moment, the local RAS inhibition by AT1 antagonist could abolish TNF-α-induced PAI-1 protein and mRNA in liver [14]. The studies are suggested that both classical and alternative RAS pathways might involve developing insulin resistance. The classical pathway is ACE-Ang-II-AT1. So, one of the previous studies was shown that AT1 inhibition could improve the oral glucose test without alteration of the plasma insulin level in diabetic animals. Indeed, Ang-II-AT1 axis

probably has a significant role in developing insulin resistance. Therefore, insulin sensitive tissue, primarily skeletal muscles could be increased glucose uptake by AT1 inhibition. This elevation is, however, thought in partly to relate to the elevated insulin-mediated IRS1-IP3-GLUT4 axis. On the contrary, it is suggested that angiotensin receptor blocker could increase insulin secretion at animals with type-II diabetes. Additionally, it is reported to enhance glucose uptake at adipose tissue, one of the sensitive insulin organs, at AT2-knockdown animals [44]. Alternative RAS pathways, ACE2/An-1-7/Mas axis, might be the high beneficial effect on diabetes based on enhancing glucose reuptake, diminishing glycogen production, and insulin resistance in hepatocytes via Akt/PI3K/IRS-1/JNK insulin signaling. Also, Ang-1-7 declines inflammation factors from adipose tissue in obese animal [18].

Giving that there might be a relationship aldosterone and insulin, systemic RAS could, also, participate in developing insulin resistance. Because aldosterone could cause insulin resistance based on its hypokalaemia effect on pancreatic beta cells, and also its direct action on insulin receptor, elevation gluconeogenesis at the liver, and sodium-glucose cotransporters. The other possible effect of aldosterone is suggested to enhance oxidative stress and inflammation in pancreatic beta cells and cause insulin resistance in adipocytes tissue. Interestingly, aldosterone is emphasized to affect insulin metabolism in liver, cardiovascular, renal, adipose, and muscle tissues. Insulin enhances angiotensinogen expression in the liver [45].

2.4.7. The local renin-angiotensin system in liver and liver cirrhosis

The role of RAS in liver cirrhosis was shown to enhance intrahepatic pressure via AT1 by experimental and human cirrhosis. Ang-II gives rise to contract and proliferates of HSC. There has been indicated that an increase of intracellular calcium ion due to the production of ROS, release of proinflammatory cytokine and chemokines lead to activate Kupffer cells. These cytokines, thus, could destroy hepatocytes and modulate extracellular matrix remodeling. Moreover, TGF-β could transform from HSC to myofibroblast, so it plays a crucial effect on the development of fibrosis. Kupffer cells are part of the reticuloendothelial system (80–90%) and thus are a primary source of cytokines. These cytokines might activate HSC, resulting in the production of ECM components, such as TGF-β, fibronectin. Ang-II is reported to develop fibrosis by proinflammatory cytokine. Also, Ang-II triggers to the mononuclear cell to synthesize more cytokines, especially TGF-β. Moreover, Kupffer cells have shown to express some RAS components, including renin, ACE, and AT1 [34].

2.4.8. The local renin-angiotensin system in liver and ischemia/reperfusion injury

Local RAS is reported to play a vital role in I/R injury in the liver. Angiotensinogen, renin, and ACE were indicated to involve in I/R injury in the liver. So, ACE inhibition could have a positive impact on I/R injury due to liver transplantation. Also, ACE might participate to inflammation, fibrosis, and anoxemia of local tissue. ACE2 is newly discovered homology of ACE and can transform Ang-II to Ang1-7 which can antagonize Ang-II's vasocontraction effects. When ACE2 is a knockdown, resulting in markedly elevating of Ang-II's expression therefore, it is suggested that ACE2 and ACE can antagonize each other. But this correlation between ACE2 and ACE has not been found at liver transplantation yet. It might be due

to complication factors interaction of liver transportation, and therefore more studies need to evaluate to reveal this complicated interaction in liver pathologies. But, up to now we know that ACE2 plays a negative role in RAS. Furthermore, local ACE2 is thought to relate to tissue hypoxia as well. In parallel, the expression and activity of local ACE2 are found to significantly elevated in the lighting biliary tract in rats and human hepatic cirrhosis and other chronic hepatic injuries. The hypoxia is believed to have significant contribution in the increase of ACE2 expression, and upregulation of its may participate some protective mechanisms against hypoxia conditions. However, healthy liver tissue just is of a trace expression of ACE and ACE2, but their mRNA and protein expressions have been elevated in the transplanted liver of rats. ACE might relate to inflammation due to Ang-II which increases the production of TNF, CINC-1, and ICAM-1 in tissue via AT1. So, ACE inhibition reduces I/R injury after experimental liver transplantation by the inflammatory promotion process. Also, it is reported that renin expression elevated fivefold after reperfusion following the I/R model by clamping the portal vein. According to the findings authors concluded that renin significantly enhanced at the initial stage of liver transportation, resulting in elevation of Ang-I. These elevations lead to increase ACE expression, eventually increasing Ang-II which gave rise to diminish blood supply in transplanted liver and aggravates the liver hypoxia, combine with inflammation [46].

2.4.9. The local renin-angiotensin system in liver and liver fibrosis

There are many pathologies of liver to cause liver fibrosis, such as alcohol, nonalcoholic fatty liver, chronic hepatitis B, and C. Liver fibrosis's characterization is related to accumulate matrix proteins in the tissue, including elastin, collagen, basement glycoproteins, proteoglycans, hyaluronan, and finally changing of the matrix composition. Under normal physiologic conditions, Disse space in the liver just has proteoglycan, nonfibril forming collagens, such as type IV, VI, and XIV and also glycoprotein, i.e., fibronectin, laminin, and tenascin. But, under the pathophysiologic conditions, these spaces have some alternation with enhancing fibronectin and tenascin, then the accumulation of Type I, Type III collagen, elastin, and laminin. Thereby, liver parenchyma has to be remodeled to accumulate bands of scar tissue. HSC in the liver is a perivascular mesenchymal cell, the chiefly fibrogenic cell-type. One of its primary functions is retinoid (vitamin A) storages under normal physiologic conditions. However, HSC shifts into interstitial myofibroblast which can produce ECM components, profibrotic and proinflammatory cytokines and chemokines under the pathophysiologic condition, such as liver fibrosis. The activation of HSC can be triggered by responding to paracrine trigger from its surrounding cell-like hepatocytes and Kupffer cells as well as alternation of ECM. These process can be maintained by some factors and autocrine profibrogenic triggers, i.e., TGF-β 1 and platelet-derived growth factor. Nowadays, a well-established pivotal participant of both inflammatory cells and activated HSCs is Ang-II [6]. Ang-II can start a proliferation of myofibroblast and stellate cells, resulting in initiate inflammatory cell and release some profibrotic molecules, i.e., TGF-β, CTGF, and IL-1β. Both human and animal studies reported that overexpression of some component of RAS was found at fibrotic liver which is related to between Ang-II and TGF-β1 [47]. It suggests that inhibition of hepatic RAS has a beneficial effect on suppressing steatosis and fibrosis [12]. Therefore, increasing of Ang-II levels in liver tissue is tightly associated with fibrosis [32].

There is some evidence indicated that both classic and alternative RAS might play a role in the development of liver fibrosis. ACE-Ang-II-AT1 axis, classic RAS, is reported to be most important for developing liver fibrosis (**Figure 3**). There is an exciting agreement that the drugs of ACE and AT1 inhibitors have been succeeding to heal of liver fibrosis by downregulation of some keys cytokines and inflammatory elements. The infusion of Ang-II is reported to cause bile duct epithelial cell proliferation, and exacerbation of liver fibrosis in rats with the bile duct ligation, resulting in to have the contribution of both local and systemic RAS. Also, Ang-II has a potential effect on cell growth and fibrosis which is critical processes of inflammation and wound healing as well. This process is activated HCSs by Ang-II though AT1. Moreover, when Ang-II incubates with activated HCS, it is shown to enhance intracellular calcium concentration, cell contraction, cellular proliferation via mitogen-activated protein kinase pathways. Ang-II in human HSCs causes profibrogenic effects on ROS generation via NADPH oxidase. NADPH oxidase is also expressed in Kupffer cells, sinusoidal endothelial cells that have to participate in developing fibrosis by ROS production as well. Hepatic fibrosis also related to the local RAS's effect on extracellular matrix (ECM) which has a balance between ECM output and degradation by two enzymes. The name of these two enzymes is matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP), which produce and degrade ECM, respectively. The balance equals to 1:1. The Ang-II can run to balance favor of TIMP1 in HSCs via AT1, induction of protein kinase C. ACE or AT1 inhibitors, therefore, can make a balance again between these two enzymes in animal models of fibrosis. The other profibrotic effects of Ang-II depend on amplification of inflammatory response, inducing acute-phase reactants, ROS, releasing of inflammatory and fibrotic cytokines including IL6, IL1, TGF-β, TNF-α chronic, and ECM deposition in liver injury. It has also induced monocyte chemoattractant protein-1 (MCP-1) and IL-8 from HCS. MCP-1 triggers leucocytes for fortification and activation. MCP-1 could be upregulated its genes by Rho intracellular pathways via Ang-II and AT1 axis. Ang-II can upregulate genes by activator protein-1 (AP-1), signal transducer, and activator of transcription (STAT) and NF-κB, which have proinflammatory efficiency, e.g., IL-6. Ang-II and NF-κB are reported to have a kind of positive feedback interaction on triggering the transcription of angiotensinogen via AT1. Kupffer cells might participate in this proinflammatory effect of Ang-II by AT1. In other words, activated Kupffer cells by Ang-II in the alcoholic liver disease generate TGF-β and TNF-α. That is why these proinflammatory effects of the Kupffer cell could be declined by AT1 but not ACE inhibitors. This finding suggested that AT1 in Kupffer cell is a pivotal role in Ang-II's inflammatory effect [6]. Human studies of fibrotic treatment are reported to have difficulties based on the requirement of taking multiple biopsies from the patient. This brings an enormous ethic problem and also makes the patient suffering from pain. This cannot be acceptable for anyone. The other difficulties of human studies is related to the illness progression very slow in the most disease, e.g., hepatitis-C, nonalcoholic liver disease. This slow progression makes it difficult to determine of therapeutic beneficial of treatment. It may overcome when the studies are planned for tracking patient for many years [6].

Fibrosis is a complicated process including collagen-I accumulation, epithelial to mesenchymal transition (EMT). EMT triggered by TGF-ß1 is a kind of structural and cellular alteration leading to separate cells, lose cell polarity, and gain cell adhesion, resulting in facilitating cell

motility. Responding to EMT, the extracellular matrix could be exposed to change for allowing cell motility and express some growth factors, e.g., VEGF. Ang-II elevates TGF-ß1 level, α-smooth muscle actin and decreases E-cadherin. The fibrosis development after hepatic bile duct ligation is reported to participate in both Ang-II and Ang-1-7. According to these findings, although Ang-II levels increase in the first week after bile ligation, Ang-1-7 levels enhance after 3 weeks of bile ligation. It also emphasized that Ang-II tends to back to its normal level after 1 week, but Ang-1-7 maintained its priority after 2 weeks [5]. On the basis of these findings, it will be concluded that classical pathways of RAS, ACE-Ang-II-AT1 has involved in the development of liver fibrosis more than alternative RAS pathway, ACE2-Ang-1-7-Mas (**Figure 2**).

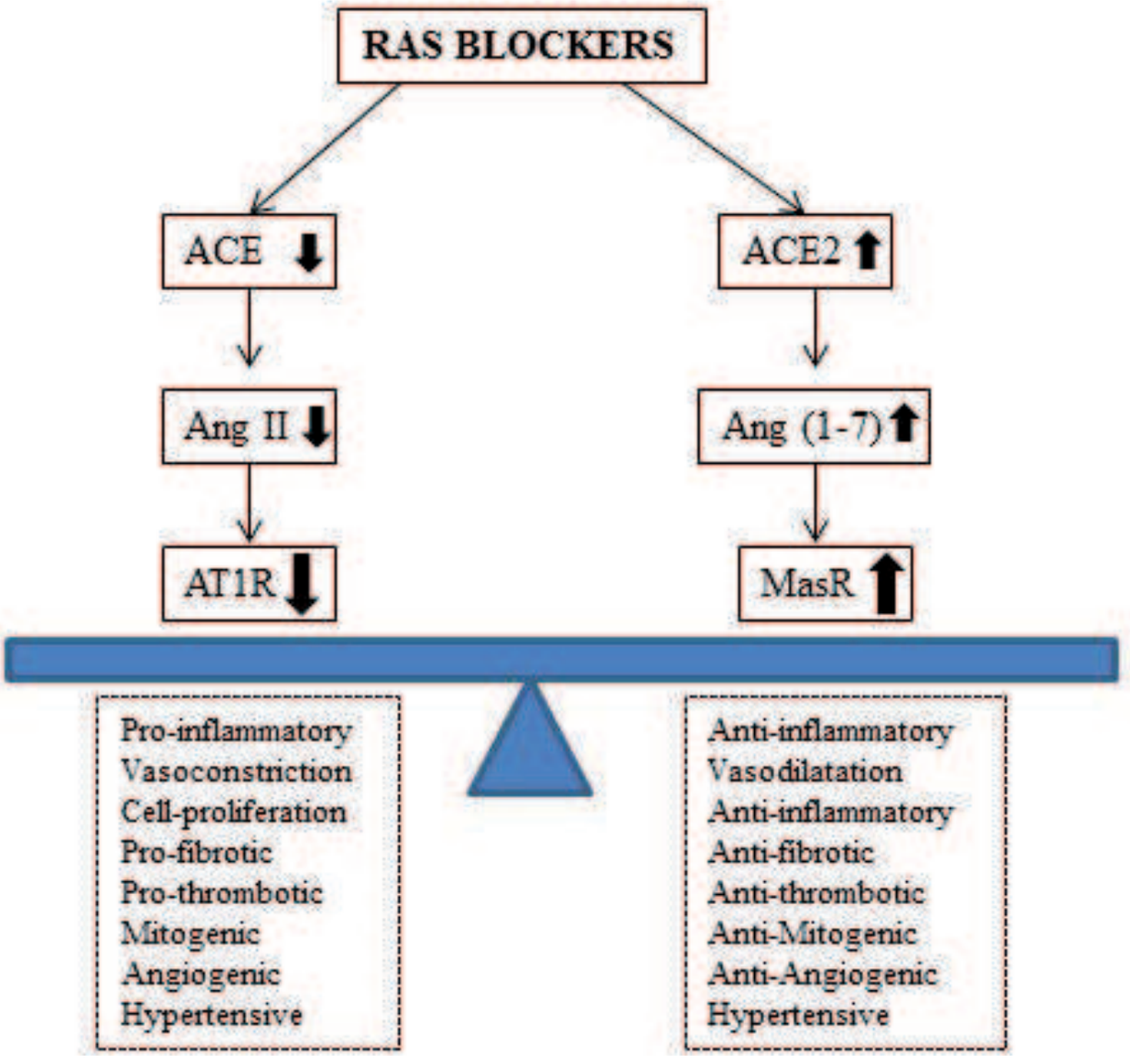

Figure 3. The effect of classical and alternative renin-angiotensin system and the effect on renin angiotensin system blockers. The figure was modified from Refs. [6, 18].

2.4.10. The local renin-angiotensin system in liver and nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a predominantly chronic hepatic disease in developed countries, and its prevalence is around 10–24% in the countries. The disease is linked to some illness, including obesity, hyperlipidemia, hypertension, type-2 diabetes, and insulin resistance (IR) [12], thus hepatic function could be elevated by losing weight [48]. In particular, there is a significant interaction between NAFLD and IR, also named metabolic syndrome that has found approximately 95% NADFLD patient. NADFLD has reported elevating inflammation and oxidative stress, leading to release inflammatory cytokines and abnormal lipoprotein [12]. Because metabolic syndrome is related to accumulate enormous triglycerides in the tissue, it is shown that ACE antagonist by drugs could help to lose the weight in an obese patient [48]. Additionally, according to one of experimental study, the liver was indicated to gain weight when fed the high-fat diet for 12 weeks. In contrast, ACE inhibition by perindopril was shown to reduce the liver weight and food consume as well. The authors suggested that low-food intake might be concerned with Ang-II and corticotropin-releasing hormone (CRP), anorexic brain peptide. Ang-II receptors were reported to express at CRP-containing neurons. Thus, Ang-II is thought to decline CRP expression from the neurons. Local Ang-II could cause to release leptin from isolated adipocytes; ACEI could block the releasing of leptin. One of the novel results of authors was that ACE activity is high in rat with obese-induced by high-fatty acid diet. They thought that elevation of ACE in liver led to accumulate triglyceride. Also, they speculated to associate with elevation ACE and developing insulin resistance and type-2 diabetes. They implied when ACE could be pharmacologically antagonized; insulin signaling could be modified in the liver, resulting in triggering insulin receptor and enhancing glucose uptake by elevation bradykinin based on decline cleavage by ACE [48]. Indeed, liver function is also affected by systemic RAS.

Ang-II plays a significant role in the development of liver inflammation and fibrosis. So, when Ang-II is blocked by ACE and ACE antagonist drugs, it helps to modify some factors, e.g., decreasing cytokine production such as TNF-α, decreasing TGF-β, elevation of adiponectin, insulin, and insulin signaling at the cellular level as well as limiting the HSCs activity. HCS in the healthy liver has very low concentration of RAS elements, but the cell increases the RAS expression, e.g., ACE, AT1 under the pathophysiologic circumstance. After activation of HCS, the cell could produce Ang-II which led to trigger some fibrogenic effects, such as cell migration, proliferation, inflammatory cytokine, and collagen secretions through commonly AT1 [12]. Ang-II's fibrogenic effects in the liver, kidney, and also heart are concerned with TGF-β. Therefore, RAS inhibition is reported to the therapeutic effect on liver fibrosis and inflammation based on NAFLD. The oxidative stress levels are reported to relate to NAFLD and also IR severity. It is shown to enhance some factors, including TNF-α, TGF-β, plasminogen activator-1, IL6, and CRP at the patients with NAFLD [12].

Additionally, the liver might be affected by cardiorenal metabolic syndrome (CRS) and type-2 diabetes mellitus based on metabolic toxicities with the development of the nonalcoholic fatty liver disease or steatohepatitis. The liver tissue has occurred some cellular remodeling during those pathologies. In the beginning, hepatocytes increase the fat accumulation as a result of lipolysis, triglycerides, and free fatty acids. Accumulation of fat triggers oxidative stress and

ROS production. Two hypotheses have been proposed to elucidate nonalcoholic fatty liver disease progression. The first theory is associated with CRS causing to the development of steatosis. The second approach is associated with hepatocytes injury, inflammation, and fibrosis, which causes mostly oxidative stress, elevated cytokines synthesis. The development of fibrosis and accumulation of ECM predominantly rely on HCS activity, a sinusoidal pericyte cell. HCS led to accumulate type-I and type-III collagen around hepatic sinusoids, probably resulting in destroying the structural and function of sinusoidal and endothelial cell-hepatocytes. Local RAS in the liver has shown to play a major role in the development of liver fibrosis. That is why Ang-II blockage could be attenuate oxidative stress, steatosis, inflammation, and fibrosis[2]. Those studies were pointed out the role of systemic RAS in NADFLD. We can speculate that there is no available research directly indicated the local RAS in liver. While Ang-II could involve a kind of NADFLD, it still needs also to evaluate the role of local RAS in liver.

2.4.11. The local renin-angiotensin system in liver and acute liver failure

Paracetamol is one of the commonly utilized drugs as a painkiller and for decreasing fever when it is used at therapeutic doses. It caused hepatotoxicity when it overdoses, a worldwide problem, resulting in acute liver failure. The drug's metabolized process is mainly carried out at liver and converted to it nontoxic metabolites which extracted by urine. But, its small proportion usually less than 5% is also metabolized by the cytochrome P450 (CYP) enzyme system (generally CYP2E1), and converted to it highly reactive metabolite, named as N-acetyl-p-benzoquinone imine (NAPQI). Its reactive metabolite leads to a toxic effect through oxidative stress. NAPQI covalently binds intracellular proteins based on its reactive electrophilic property. Although NAPQI reacts with reduced glutathione (GSH) shifting to nontoxic metabolites at its therapeutic dose, it also reacts with GSH at high doses of paracetamol, but GSH could not have enough level of enormous reactive metabolites, resulting from oxidative stress and mitochondrial dysfunction. GSH is one of the vital antioxidant enzymes for suppressing of the oxidative compound. A decline of GSH could cause mitochondrial oxidative, depress mitochondrial respiration, and adenosine triphosphate deprivation, resulting in hepatocytes and sinusoidal endothelial cells necrosis. Ang-II is well documented to exaggerate oxidative stress. So, Ang-II blocked by aliskiren, renin inhibitors, is reported to decline acute toxicity of liver-induced by paracetamol by decreasing oxidative stress. Moreover, aliskiren is shown to reduce elevated TGF-α and downregulate activated Kupffer cells and HSCs at the acute liver injury induced by paracetamol [49].

3. Conclusion

After recognition of local RAS, the new insight of RAS is shifted to local or tissue due to its endocrine function. Systemic RAS may not play important role under pathophysiologic conditions but local RAS may play a crucial role under pathophysiologic conditions, especially independent and/or dependent systemic RAS. The studies have shown that local RAS in the liver has a crucial role not only in maintaining the physiologic functions but also in developing pathophysiology. There are limited studies available to evaluate local RAS under

a pathophysiologic circumstance. The component of local RAS may present a small amount expression in the normal liver tissue. However, its component expressions are increased under a pathophysiologic condition, leading to enhance of importance and effects of RAS in the tissue. So, some pathophysiologic conditions have been indicated to relate to local RAS, such as liver fibrosis, portal hypertension, insulin resistance, liver cirrhosis, cancer growth, and metastasis. That is why the new studies are needed to evaluate the local RAS under a pathophysiologic condition.

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