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Angiotensin II: a key mediator in the development of liver fibrosis and cancer

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Abstract

Background: Liver fibrosis and its outcomes of cirrhosis and hepatocellular carcinoma are major worldwide health problems and due to the complicated molecular pathogenesis, the options for effective systemic cure are relatively restricted. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, having well established safety profiles and low economic costs, may provide synergistic effects to existing chemotherapies by reducing angiotensin II-mediated angiogenesis, fibrogenesis, mitogenesis, metastasis, and oxidative stress.

Conclusion: These effects suggest angiotensin II inhibitors as promising agents for further clinical trials in the management of patients with fibrotic diseases.

Keywords: Fibrosis, Hepatocellular carcinoma, Renin-angiotensin system, Angiotensin II

Introduction and aim

Owing to the complex molecular pathogenesis of fibrosis and its outcomes of cirrhosis and hepatocellular carcinoma, the possibility for effective systemic treatment is relatively limited. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may provide synergistic effects to existing chemotherapies by reducing angiotensin II-mediated angiogenesis, fibrogenesis, mitogenesis, metastasis, and oxidative stress along with dilation of the tumor vessels, leading to improved overall drug delivery.

Hepatic fibrosis

Long-lasting liver damage due to various etiologies is the leading cause of liver fibrosis. It is primarily characterized by increased accumulation and unbalanced degradation of extracellular matrix (ECM) (Beljaars et al. 2002; Baiocchini et al. 2016). Around six times more ECM than normal is found in the liver at progressive stages, including collagens I, III, and IV. Reduced activity of metalloproteinases (MMPs), the main ECM-removing mediators, is predominantly due to an overproduction of tissue inhibitors of metalloproteinases (TIMPs), which are the specific inhibitors (Arthur 2000; Arpino et al. 2015). ECM proteins interfere with the hepatic architecture when they are developed by building up fibrous scars (Parsons et al. 2007); ultimately, the development of nodules of regenerating hepatocytes characterizes the framework of cirrhosis (Schuppan and Afdhal 2008). Owing to the high prevalence of fibrosis and cirrhosis in the general population (Poynard et al. 2010), molecular abnormalities of the liver and their relation to fibrosis have been of particular interest (Karsan et al. 2004).

Liver fibrosis is a result of the wound-healing response to repetitive cycles of damage and repair in the liver in which parenchymal cells regenerate and substitute the necrotic tissue (Hayes and Chayama 2016). Concomitant with these processes, an inflammatory response and a regulated deposition of ECM are established. If the damage persists, then eventually liver regeneration is failed, with the replacement of parenchymal cells with excessive ECM. As these fibrotic changes continue, a transition from collagen bands to bridging fibrosis to frank cirrhosis happens (Bataller and Brenner 2005; Sayyed et al. 2016).

Hepatic stellate cells (HSCs) are the principal ECM-producing cells of the damaged liver (Gabele et al. 2003; Hyun et al. 2016). Normally, HSCs exist in the space of Disse. Following persistent hepatic injury, they differentiate into myofibroblast-like cells of

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pro-inflammatory and fibrogenic activities (Milani et al. 1990; Marra 1999; Schon et al. 2016). Upon activation, HSCs travel to the sites of damage and repair and starts to produce and secrete large amounts of ECM (Lindquist et al. 2000; Wang et al. 2016).

Injured liver produces reactive oxygen species (ROS) and fibrogenic mediators and provokes the recruitment of white blood cells by inflammatory cells (Lan et al. 2015). Apoptosis of parenchymal cells stimulates the fibrogenic activities of myofibroblasts. Polymorphnuclear leukocytes and lymphocytes induce HSCs to produce and secrete collagen. HSC transactivation is also influenced by paracrine cytokines, platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), etc. that are synthesized by kupffer cells (KCs). Further, chemokines and cell adhesion molecules and their receptors are expressed by activated HSCs (Vinas et al. 2003; Riether et al. 2015). Therefore, inflammatory and fibrogenic cells stimulate each other and a complex interaction occurs in the course of liver fibrogenesis between different hepatic cell types (Maher 2001).

Cytokines have a major pro-fibrotic role in regulating liver fibrogenesis in response to injury in vivo and in vitro (Marra 2002). Amongst them, TGF-β1 appears to be a central mediator in hepatic fibrogenesis (Gressner et al. 2002). TGF-β favors the transactivation of HSCs into myofibroblasts and prevents ECM degradation. Strategies aimed at inhibition of TGF-β1 synthesis and/or signaling markedly ameliorated liver fibrosis in experimental models (Shek and Benyon 2004; Xu et al. 2016).

In addition, PDGF, TNF-α, interleukin (IL)-6, IL-1β, and IL-13 are also key pro-fibrotic mediators, pharmacological inhibition, and/or gene deletion of these cytokines prevented the progression of hepatic fibrosis (Schwabe et al. 2003; Kaviratne et al. 2004; Sudo et al. 2005). Furthermore, vasoconstrictors (e.g., norepinephrine, angiotensin II (Ang-II)) (Oben and Diehl 2004; Han et al. 2017), and endothelin (ET)-1 (Cho et al. 2000; Correia-Costa et al. 2016) exert potent fibrogenic activities, while vasodilators (e.g., nitric oxide (NO), relaxin) have opposite actions (Iwakiri 2015).

Ang-II is a vasoactive component of the renin-angiotensin system (RAS) that seems to play a principal role in hepatic fibrosis (Iwakiri 2015); it induces production of inflammatory cytokines, mitogenesis, proliferation, and collagen synthesis in activated HSCs (Bataller et al. 2003a). Inhibition and/or gene knockout of Ang-II significantly attenuated experimental liver fibrosis (Yao et al. 2004a). Notably, the main components of RAS are expressed in injured liver tissues locally (Ahmadian et al. 2016), and activated HSCs can synthesize Ang-II (Yoshiji et al. 2002a).

RAS contribution to fibrosis development

Angiotensin-converting enzyme (ACE) catalyzes the conversion of the Ang-I into Ang-II; several reports proposed that Ang-II plays a crucial role in hepatic fibrogenesis (Saber et al. 2018a), and an Ang-II inhibitor or receptor blocker significantly attenuated hepatic fibrosis development and progression (Rippe and Brenner 2004; Yao et al. 2004b; Saber et al. 2017; Saber et al. 2018b). ACE is synthesized by hepatic KCs and is detected at the gene level in trans-activated HSCs (Bataller et al. 2003b; Huang et al. 2015). Proliferating bile duct epithelial cells, hepatic inflammatory cells, and activated HSCs are potential sources of ACE in the bile duct ligation liver model of fibrosis (Paizis et al. 2002). The normal level of ACE expression and activity in normal liver tissue is considerably upregulated in the bile duct ligation model of rat liver (Paizis et al. 2002). The distribution of liver ACE is generally found increased in areas of active fibrogenesis following bile duct ligation. In addition, the increased serum activity of ACE in cirrhotic patients suggests also that ACE has a critical role in hepatic fibrosis (Huskic et al. 1999; Noguchi et al. 2017).

Blockade of Ang-II can inhibit the progression of hepatic fibrosis in animal models (Yoshiji et al. 2005). Perindopril and candesartan were found to attenuate hepatic fibrosis and reduce the expression of alpha smooth muscle actin (α-SMA) (Yoshiji et al. 2001a) and TGF-β1 (de Oliveira da Silva et al. 2017). Captopril delayed the progression of hepatic fibrosis in a model of rat bile duct ligation and was strongly associated with a decrease of collagen gene expression and TGF-β1 (Jonsson et al. 2001). TGF-β1 expression upregulated by Ang-II parallels overproduction of ECM proteins (Yoshiji et al. 2001a; Sui et al. 2015). Ang-II also upregulates α-SMA (Meng et al. 2015) and downregulates E-cadherin (Nguyen et al. 2016), both of which control epithelial mesenchymal transition (EMT) (Liu et al. 2007).

Tissue inhibitors of metalloproteinases, particularly the TIMP-1, are markedly increased both in humans and murine liver fibrosis (Arpino et al. 2015; Iredale 1997). TIMP-1 was found to boost the development of hepatic fibrosis in a transgenic mouse model (Yoshiji et al. 2000). A marked reduction in the TIMP-1 expression level was linked to resolution of fibrosis following matrix remodeling in a rat model of hepatic fibrosis (Iredale et al. 1998). In addition, the TIMP-1 expression level was significantly upregulated by Ang-II in hepatic myofibroblasts in a time- and dose-dependent manner (Caley et al. 2015). Parallel to TIMP-1 inhibition perindopril significantly attenuated hepatic fibrosis development. Moreover, Candesartan and LY333531 (a protein kinase C (PKC) inhibitor) abolished TIMP-1 mRNA increase by Ang-II in a dose-dependent manner suggesting PKC signaling

pathway in the fibrogenic effect of Ang-II (Yoshiji et al. 2003).

It was found that Ang-II increased TGF-β and fibronectin mRNA expression in KCs that found to express the angiotensin II type 1 (AT1) receptor (Leung et al. 2003). One report stated that KCs induced with Ang-II demonstrated marked increase in the mRNA expression levels of TGF-β1, TNF-α, and fibronectin, and these levels were effectively decreased by saralasin and losartan (Leung et al. 2003). Therefore, Ang-II has a critical role in the fibrotic process and the interaction of Ang-II and AT1 receptor is one of the foremost regulatory pathways in the development of liver fibrosis.

Mast cells are capable of producing TGF-β1 and ECM components. AT1 receptor was found expressed in liver mast cells in the murine bile duct ligation (BDL) model of liver fibrosis (Paizis et al. 2002).

Angiogenesis is a vital process in both hepatic fibrogenesis (Ehling et al. 2014) and carcinogenesis (Vogten et al. 2004; Dimova et al. 2014). Vascular endothelial growth factor (VEGF) receptor expression was found to be upregulated in a murine model of hepatic fibrosis (Iwakiri et al. 2014). VEGFR (VEGF receptor)-1 and VEGFR-2 neutralizing monoclonal antibodies markedly attenuated fibrosis development through suppression of neovascularization (Yoshiji et al. 2002b). Furthermore, experimental fibrosis was inhibited by the anti-angiogenic agents, angiostatin and TNP-470 (Vogten et al. 2004). Pro-angiogenic properties of Ang-II are in part facilitated by potentiating the expression of VEGF in endothelial cells (Imanishi et al. 2004).

Alpha smooth muscle actin-positive cells were significantly reduced in count by candesartan and perindopril. Ang-II activates nuclear factor kappa-B (NF-κB) pathway via AT1Rs leading to gene transcription of pro-inflammatory cytokines such as TNF-α, IL-6, and TGF-β1 (Wolf et al. 2002; Ozawa et al. 2007; Ruiz-Ortega et al. 2006).

The interactions of Ang-II and AT1Rs are connected to certain cardiac and renal fibro-proliferative diseases (Bascands and Schanstra 2005; Sakai et al. 2008). A normotensive mouse model of renal fibrosis found that both ramipril and candesartan postponed the onset and abolished the increase in the magnitude of proteinuria and increased survival (Gross et al. 2004).

Hepatocellular carcinoma

Hepatocellular carcinoma is the most widespread type of primary liver lesions, and it is the main consequence of cirrhosis. Numerous risk factors including hepatitis C virus (HCV) and hepatitis B virus (HBV) infections are the main causes of high prevalence of HCC (El-Serag 2007; Nordenstedt et al. 2010; Sherman 2005; Mancuso 2017).

RAS contribution to cancer development

At a local tissue level, RAS enhances tumor growth. Immune modulatory effects (Abdel-Ghany et al. 2015), angiogenesis, mitogenesis, and ECM formation lay behind potential tumor-promoting effects of RAS (Deshayes and Nahmias 2005). Components of the RAS are frequently found overexpressed in several types of cancers such as lung, skin, cervical, pancreatic, prostate, brain, colon, and breast cancer compared to their corresponding normal tissues (Deshayes and Nahmias 2005). In particular, upregulation of the AT1R is principal. However, the expression of RAS components appears to be altered with tumor types and their grade (Louis et al. 2007).

Modulation of angiogenesis is the principal mechanism by which RAS achieves its pro-tumor effects, which is an essential step in the development of solid tumors (Saber et al. 2018c). Various pro-angiogenic mediators are activated by Ang-II including VEGF (Huang et al. 2008), angiopoietin-2 (Yasumatsu et al. 2004), basic fibroblast growth factor (b-FGF) (Wysocki et al. 2006), and platelet-derived growth factor (PDGF) (Fujita et al. 2002); these angiogenic properties are mediated by the AT1R. In addition, RAS inhibition is often accompanying a reduction in the expression of VEGF (Uemura et al. 2003; Kosaka et al. 2007; Saber et al. 2018d). In a model of ischemia-induced angiogenesis, Ang-II induces angiogenic effects in the damaged vessels by increasing expression of VEGF and upregulating endothelial NO synthase levels; these effects found to be mediated through the AT1R (Tamarat et al. 2002).

In a murine model of HCC, angiotensin-converting enzyme inhibitors (ACEIs) have inhibited the development of HCC lesions (Yoshiji et al. 2001b). Perindopril showed a reduction in angiogenesis and tumor progression in head and neck squamous cell carcinoma (Yasumatsu et al. 2004). Also, candesartan diminished angiogenesis in different types of cancers such as the xenograft model of human prostate cancer (Kosaka et al. 2007), mouse melanoma syngeneic tumors (Egami et al. 2003), ovarian cancer cells (Suganuma et al. 2005), and murine Lewis lung cancer model (Fujita et al. 2002). In addition, captopril and irbesartan inhibited angiogenesis, carcinogenesis, and metastases in colorectal cancer liver metastases in mice (Neo et al. 2007). Therefore, RAS intensely impact the level of neovascularization.

Yoshiji et al. (2007) revealed that a dual combination of ACEI and vitamin K produced intense anti-angiogenic properties and ameliorated dysplastic nodules and effective reduction in the level of alpha fetoprotein (AFP) in cirrhotic patients; these nodules disappeared completely after 1 year of administration. Another combination of perindopril and vitamin K2 prevented neovascularization and the development of HCC in a report by Yoshiji et al.

(2006). In addition, Yoshiji et al. (2002c) revealed that perindopril effectively ameliorated hepatic fibrosis and pre-neoplastic foci in two models of liver carcinogenesis. In addition, perindopril and interferon-β at lower clinical effective doses inhibited angiogenesis and prevented tumor development that was associated with a reduction in VEGF (Noguchi et al. 2003). Furthermore, perindopril and 5-fluorouracil prevented the development of HCC by suppressing neovascularization in mice (Yanase et al. 2007).

In the clinical settings, it was reported that patients treated with sorafenib plus RAS inhibition had a better median overall survival (19.5 months) compared to those treated with either sorafenib (10.9 months) or RAS inhibition (9.7 months) alone ($p = 0.043$) (Pinter et al. 2017). Another study reported that the use of ARBs during erlotinib treatment may prolong overall survival of metastatic non-small cell lung cancer patients (Aydiner et al. 2015).

Ang-II can increase expression of ETB receptor in HSCs and induce production of ET-1 in endothelial cells (Bataller et al. 2003b; Cheng et al. 2005). ET-1 acting on ETB receptor can induce migration and proliferation of endothelial cells. Several studies proposed that ET-1 augments the pro-angiogenic effects of VEGF (Ribatti et al. 2007).

Ang-II is able to induce mitogenesis of endothelial cells, fibroblasts, and smooth muscle cells (Touyz and Schiffrin 2000) and can induce transcription of several growth-related oncogenes (Nogueira et al. 2007) and growth factors (Deshayes and Nahmias 2005) in various cells. These suggest that RAS can also affect tumor cell proliferation and survival.

Ang-II stimulates the secretion of gonocyte colony-stimulating factor (GCSF), MCP-1, and MCP-2 resulting in excessive macrophage infiltration (Egami et al. 2003; Kosugi et al. 2006; Tone et al. 2007). In addition, macrophage infiltration into the tumor endorses growth and metastasis (Leek et al. 1994; van der Bij et al. 2005). Notably, M2 macrophage pathway is connected with these pro-tumor functions.

In addition, macrophage infiltration can participate in tumor metastasis at later stages when host defenses are debilitated. Regarding this situation, rapid proliferation of cancer cells enable binding of tumor cells by KCs to initiate the generation of new metastatic sites (Bayon et al. 1996). Macrophages also can secrete several cytokines facilitating tumor growth and metastases by induction of angiogenesis (Egami et al. 2003; van der Bij et al. 2005; Nishie et al. 1999).

Conclusion

A feature is now becoming clear that there is a prerequisite of using multiple drug therapy for management of liver fibrosis and HCC. This is due to the complex networks of multiple and often redundant pathways. Anti-hypertensive agents based on angiotensin II inhibition such as the ACEIs or the ARBs are of low economic cost and have already been in clinical use with their well-known safety profiles and if these drugs can inhibit the development and progression of tumors at their lowest effective clinical doses, then they may provide a useful adjunctive therapeutic strategy in the treatment of fibrosis and cancer. Therefore, angiotensin II inhibitors are promising candidates for further clinical trials in the management of liver fibrosis, cirrhosis, and HCC.

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