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Commentary
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Angiotensin-(1-7) and the Regulation of Anti-Fibrotic Signaling Pathways

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Commentary

Angiotensin-(1-7) (Ang-(1-7)), an alternative product of the renin-angiotensin system (RAS), was initially identified in the circulation, brain and adrenals by our laboratory over 25 years ago and was originally considered to modulate the constrictor and pressor actions of Angiotensin II (Ang II) [1]. However, the experimental evidence to date suggests that Ang-(1-7) exhibits a wide range of protective effects apart from the regulation blood pressure [2,3]. Circulating Ang-(1-7) is derived by the direct conversion of the inactive precursor peptide Ang I by the metalloendopeptidase (MEP) neprilysin while the cellular levels of the peptide may reflect processing of Ang I by another MEP - thimet oligopeptidase; both enzymes hydrolyze the Pro7-Phe8 bond of Ang I to generate Ang-(1-7) [4]. Endogenous levels of Ang-(1-7) may also originate from the direct conversion of Ang II by mono-carboxypeptidases angiotensin converting enzyme 2 (ACE2) and prolyl carboxypeptidase [4]. These latter pathways initially require the conventional processing of Ang I by ACE to generate Ang II; however, ACE is the principal pathway in the circulation to degrade Ang-(1-7) to Ang-(1-5) and explains the pronounced effect of ACE inhibitors to augment the circulating levels of Ang-(1-7) [5]. Elucidation of the processing steps and unique actions of Ang-(1-7) has ostensibly led to the divergence of the RAS into multiple functional arms that include the ACE-Ang II-AT1 receptor (AT1R) and the ACE2/MEP-Ang-(1-7)-AT7/MasR [2,3].

In contrast to the Ang II-AT1R that mediates a number of pathological events associated with an "activated RAS", the Ang-(1-7) pathway is thought to antagonize many of cellular actions of the Ang II-AT1R axis [3]. In this regard, the pathologies typical of an activated RAS such as inflammation, fibrosis and an altered redox balance may well reflect a stimulated Ang II-AT1R and an attenuated Ang-(1-7)-AT7R axis [6]. Therapeutic approaches to block the ACE-Ang II-AT1R that include ACE inhibitors (ACEIs) and AT1R antagonists (ARBs) increase endogenous levels of Ang-(1-7) [4]. Moreover, treatment with Ang-(1-7) may convey important therapeutic benefits in a range of pathologies including cancer, diabetes, and hypertension and tissue fibrosis [3]. The current review examines the cellular signaling pathways of the Ang-(1-7)-AT7/MasR axis that are associated with the anti-fibrotic actions of the peptide.

Angotensin-(1-7) Attenuates Fibrosis

Tissue fibrosis is a normal reparative process involved in the cellular response to tissue injury; however, progressive and sustained fibrosis in various clinical pathologies including heart failure, pulmonary hypertension, diabetic nephropathy, non-alcoholic liver disease, peripheral arterial disease, muscular dystrophy and diabetic retinopathy leads to an inevitable decline in organ function. Activation of the ACE-Ang II-AT1R is typically associated with fibrosis in multiple tissues that can reflect an increase in blood pressure and the direct cellular effects of Ang II. In turn, blockade of the RAS by ACEIs or ARBs can be an effective approach to attenuate the progression of fibrosis. Since RAS blockade may result in enhanced levels of Ang-(1-7) and/or higher expression of the AT7/MasR, an emerging number of studies have begun to directly examine the impact of exogenous Ang-(1-7) in different models of fibrosis.

Iwata et al. initially reported evidence of specific Ang-(1-7) binding sites expressed in isolated cardiac fibroblasts, a key cell type involved in tissue fibrosis; the Ang-(1-7) receptor sites were sensitive to the AT7/MasR antagonist D-Ala7-Ang-(1-7) (DALA, A779) and the non-selective angiotensin antagonist [Sar1,Thr8]-Ang II (Sarthran), but not AT1R or AT2R blockers [7]. Ang-(1-7) reduced the Ang II-dependent stimulation of 3H-proline uptake as an index of fibrosis and reduced the expression of endothelin-1 and the cytokine LIF in cardiofibroblasts, but failed to attenuate TGF-β expression, an important pro-fibrotic cytokine and downstream effector of Ang II [7]. Several reports subsequently demonstrated that exogenous administration of Ang-(1-7) attenuated the development of cardiac fibrosis in models of pressure overload induced by aortic co-arctation [8], DOCA-salt hypertension [9], chronic Ang II treatment [10,11], LNAME hypertension [12], diabetic cardiomyopathy [13] and doxorubicin-induced cardiotoxicity [14]. Importantly, treatment with the AT7/MasR antagonist DALA exacerbated the extent of Ang II-induced cardiac fibrosis and the expression of multiple cytokines including TGF-β, TNFα, MCP-1 and ICAM-1, as well the metalloproteinase inhibitors TIMP 1 and 2 suggesting that intrinsic Ang-(1-7) tone mediates the pro-fibrotic actions of Ang II within the heart [6]. The anti-fibrotic actions of Ang-(1-7) in experimental models are not limited exclusively to the heart as Ang-(1-7) administration ameliorates fibrosis in liver steatosis [15,16], pulmonary hypertension [17], pulmonary asthma [18], idiopathic pulmonary fibrosis vascular hypertension [19] muscular dystrophy [20] and both obstructive and diabetic nephropathies [21,22]. Indeed, Ang-(1-7) offered greater protective effects than the AT1R antagonist valsartan to ameliorate the diabetic nephropathy [23] and the combination of Ang-(1-7) and an ACE inhibitor was more effective than either agent alone to attenuate diabetic cardiac fibrosis [24].

Ang-(1-7) Signalling Pathways

TGF-β/SMAD

Activation of the Ang-(1-7) signal transduction pathway generally involves the MasR protein and is blocked by the specific antagonists DALA and D-Pro7-Ang-(1-7); however, AT1R, AT2R and bradykinin B2R antagonists are also reported to block some of the actions of Ang-

(1-7) suggesting either a direct interaction of these receptors with the MasR or downstream effects of an activated Ang-(1-7)-MasR on these receptor systems [3,5,25,26]. In regards to tissue fibrosis, the activation of TGF-β and the SMAD transcription factor pathway are considered a key signaling event in the initiation and progression of cellular fibrosis (Figure 1). Cai et al. reported that Ang-(1-7) attenuated SMAD phosphorylation, as well as reduced collagen, CTGF and α-SMA expression in the bile-duct ligation model of liver fibrosis [15]. Acuna et al. also find that Ang-(1-7) attenuated the TGF-β/SMAD pathway in skeletal muscle of an experimental model of muscular dystrophy [20]. Moreover, Ang-(1-7) treatment was associated with a reduction in the pro-fibrotic miRNA-21 in both the skeletal muscle and in fibroblasts isolated form the mdx rat model [20]. In renal epithelial NRK-52 cells exposed to high glucose conditions, Ang-(1-7) attenuated the increase in TGF-β expression suggesting that Ang-(1-7) may directly influence the expression of the cytokine. The inhibitory effect of Ang-(1-7) on TGF-β in the NRK-52 cells was reversed by the AT7/MasR antagonist DALA [27].

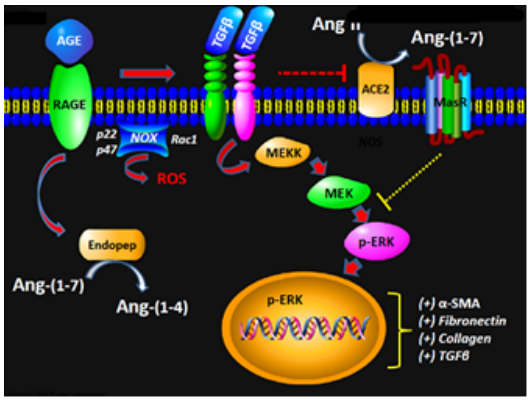

Figure 1: Potential scheme depicting the influence of Angiotensin-(1-7) on the AGE-TGF-β signaling pathway: Advanced glycation end products (AGE) binds to the receptor for AGE (RAGE) and induces TGF-β potentially by the generation of reactive oxygen species (ROS) through activation of the NADPH oxidase complex [NOX, p22phox (p22), p47phox (p47), Rac-1]. TGF-β stimulates the non-canonical pathway MAP kinase pathway to promote phosphorylated ERK1/2 to traffic to the nucleus and increase expression of EMT/fibrosis genes including α-smooth muscle actin (αSMA), fibronectin, collagen and TGF-β. The TGF-β pathway may reduce intrinsic Angiotensin-(1-7) [Ang-(1-7)] tone by downregulation of ACE2 and the AT7/Mas receptor (Mas), as well as increased degradation of the peptide to Ang-(1-4) through a soluble endopeptidase (Endopep). Ang-(1-7) attenuates EMT and fibrosis by inhibiting ERK1/2 phosphorylation potentially through the activation of intracellular phosphatases.

In addition to the canonical TGF-β/SMAD pathway, non-canonical pathways to promote tissue fibrosis include the TGFβ-dependent activation of MAP kinases [28]. Ang-(1-7) treatment attenuated the chronic stimulation of the MAP kinases ERK1/2, p38 and JNK associated with the amelioration of pulmonary fibrosis [17] and diabetic nephropathy [22]. We find that Ang-(1-7) abolished both ERK 1/2 phosphorylation and α-SMA expression in response to TGF-β in renal proximal tubule NRK-52 cells [29]. In this regard, the inhibitory effects of Ang-(1-7) on fibrosis may reflect the activation of various cellular phosphatases including SHP-1 and the dual signalling phosphatase (DUSP, MKP-1) that inactivate a stimulated MAPK pathway [30-33].

Oxidative Stress

Alterations in the cellular redox balance also contribute to tissue fibrosis that may reflect an activated TGF-β pathway. Moreover, increased oxidative stress in a positive feedback manner may promote a sustained stimulation of the TGF-β pathway [34,35]. Ang-(1-7) attenuated oxidative stress possibly through the reduction in NOX 4 expression, as well as reduced expression of the NLRP3/IL-1β in flammasone that link the anti-inflammatory actions of Ang-(1-7) to the inhibitory effects on liver fibrosis [15]. In the db/db mouse model of obesity and type 2 diabetes, the Ang-(1-7)-dependent reduction in renal fibrosis was associated with an overall reduction of oxidative stress and increased catalase activity suggesting that Ang-(1-7) stimulates scavenging pathways as well [22]. Chan et al. also find that Ang-(1-7) reduced oxidative stress and fibrosis in the kidney that was associated with the reduced expression of NOX 4, the major NADPH oxidase isoform in the kidney [36]. Indeed, Shi et al. report that Ang-(1-7) reduced the renal expression of the pro-fibrotic cytokine TGF-β, as well as the ROS-sensing proteins Nrf2 and HO-1 that may reflect an overall reduction in ROS by Ang-(1-7) [36].

The stimulation of the MAPK pathway may reflect an initial increase in reactive oxygen species (ROS) signaling upstream from MAPK and the reduction in oxidative stress by Ang-(1-7) may potentially attenuate MAPK stimulation of [37,38]. Consistent with this proposed pathway, Ang-(1-7) blocked Ang II-induced migration and TGF-β and collagen expression of pulmonary myofibroblasts associated with a reduction in ROS and NOX 4 expression [17]. Moreover, comparable effects to Ang-(1-7) on pulmonary myofibroblasts were achieved with the ROS scavenger tempol and the NAD(P)H oxidase inhibitors apocynin and DPI [17]. Although the intracellular sources of ROS in fibrosis are not well-defined, the role of mitochondrial ROS may constitute an additional pathway to the stimulation of TGF-β, EMT and fibrosis [37,39,40]. Indeed, we recently identified a MEP-Ang-(1-7)-AT7/MasR pathway in mitochondria isolated from the sheep kidney that may contribute to cellular redox balance and could potentially influence myofibroblast transition [41]. In a study of the mitochondrial proteonome, the Ang-(1-7) agonist AVE 0991 reduced the expression of proteins associated with inflammation and apoptosis in the kidneys of ApoE-/- knockout mice [42]. Increased oxidative stress appears to be key to the downstream activation of the MAPK and TGF-β/SMAD pathways that contribute to fibrosis.

Myofibroblast Transiton

An intriguing albeit controversial aspect of fibrosis is the role of myofibroblasts derived from resident epithelial, endothelial and pericyte cells, as well as fibroblasts [37,43]. Myofibroblast transition results in a more secretory and migratory phenotype that may ultimately promote tissue fibrosis, as well as depleting the local population of normal cells. TGF-β is a prominent stimulus for myofibroblast formation, and likely contributes to myofibroblast transition elicited by other agents including Ang II, advanced glycation products (AGEs), aldosterone, and endothelin, as well as hypoxic and hyperglycemia conditions [37,38,44,45]. Treatment with Ang-(1-7) reversed the epithelial to mesenchymal or myofibroblast transition (EMT) of NRK-52 cells exposed to high glucose that was associated

with reduced TGF-β expression and attenuated MAPK activation [46]. We reported that Ang-(1-7) also abolished EMT in NRK-52 cells chronically exposed to the AGE methylglyoxal albumin (MGA) [29]. Although AGE exposure increased TGF-β expression that apparently drives EMT in these cells, Ang-(1-7) failed to reverse the increase in the cellular levels of TGF-β. However, Ang-(1-7) abolished both the AGE and TGF-β induced activation of ERK 1/2 that reflects downstream activation of the non-canonical TGF-β signaling pathway; both MEK and TGF-β kinase inhibitors prevented the AGE-dependent induction of EMT [29]. In contrast, treatment with an AT1R blocker did not attenuate AGE-induced EMT or ERK activation suggesting that the cellular actions of Ang-(1-7) do not reflect the direct antagonism of the Ang II-AT1R axis in the NRK-52 cells [29].

RAS Expression

Finally, the progression of cellular fibrosis may potentially reflect both the loss of negative feedback inhibitory pathways and the gain of positive feedback systems. In regards to the RAS, AGE-induced EMT in the renal NRK-52 cells was associated with a marked reduction in the intracellular levels of Ang-(1-7) that may result in the potential loss of Ang-(1-7) tone in these cells. AGE markedly increased the cellular metabolism of Ang-(1-7) to Ang-(1-4) through an unidentified cytosolic endopeptidase and tended to reduce the processing of Ang I to Ang-(1-7) by thimet oligopeptidase [29]. Others have shown that TGF-β or AGE exposure reduces expression of both ACE2 and the AT7/MasR, but increases the cellular components of the ACE-Ang II-AT1R axis [27,47]. In this regard, Zhou et al. recently reported that blockade of the Wnt/β-catenin axis, a key signaling pathway involved in the pro-fibrotic actions of TGF-β, abrogates the activation of the RAS components renin, angiotensinogen and the AT1R, as well as attenuates renal fibrosis and myofibroblast activation in adriamycin-induced nephropathy [48]. The role of the Wnt/β-catenin pathway on the Ang-(1-7) axis including the expression of ACE2, neprilysin and the Mas receptor is not currently known.

Conclusion

In conclusion, activation of the Ang-(1-7)-AT7/MasR axis may be a potentially important therapeutic target to attenuate fibrosis in various tissues and attenuate the progressive decline in organ function, particularly in lieu of the lack of effective approaches to inhibit fibrosis. Additional studies are clearly warranted to precisely define the signaling pathways inovled in the anti-fibrotic actions of Ang-(1-7) within distinct cell types. In this regard, an evolving area is the epigenetic response that contributes to fibrosis and the development of approaches to attenuate this mechanism [49-51]; future studies should address the extent that Ang-(1-7) impacts the epigenetic signaling mechanisms in fibrosis. The current experimental approaches have predominantly relied on the native peptide; however, Ang-(1-7) exhibits a very short half-life and is rapidly cleaved by multiple peptidases including ACE and dipeptidyl peptidase 3 (DPP 3) [52,53]. Moreover, Ang-(1-7) at higher doses may function as a partial agonist at the AT1R and contribute to rather than inhibit the progression of fibrosis. In this regard, the development of orally active and cell-penetrating Ang-(1-7) agonists that are resistant to peptidases and exhibit greater selectivity among angiotensin receptor subtypes may constitute the next step to effectively combat fibrosis.

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Conflict of Interests

None declared

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