

# The Role of Endoglin in Myocardial Fibrosis

Kou-Gi Shyu

Myocardial fibrosis is closely associated with heart failure because myocardial fibrosis may cause the loss of normal cardiac function. Endoglin is a homeodimeric membrane glycoprotein, a co-receptor of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and  $\beta$ 3. Endoglin is a potent mediator of profibrotic effects of angiotensin II on cardiac fibroblasts and can modulate the effect of TGF- $\beta$ 1 on extracellular matrix synthesis. These data indicate that endoglin plays an important role in fibrogenesis in cardiac remodeling. Endoglin induced by TGF- $\beta$ 1 is largely through PI-3 kinase, Akt, Smad3/4 and endoglin promoter pathways. Endoglin was upregulated in pressure-overload, volume-overload heart failure and acute myocardial infarction and was associated with myocardial fibrosis. Silencing endoglin expression could attenuate myocardial fibrosis and improve survival in animal study. Endoglin expression was increased in failing left ventricle before use of left ventricle assist device, and reduced back to control levels after use of left ventricle assist device. Targeting endoglin may provide a potentially unique and novel therapeutic approach for reducing myocardial fibrosis in patients with heart failure.

**Key Words:** Angiotensin II • Endoglin • MicroRNA • Myocardial fibrosis • TGF- $\beta$ 1

## INTRODUCTION

Heart failure is one of the most common causes of hospitalization in the United States and is the predominant disease in the elderly.<sup>1,2</sup> Heart failure is also a major cause of morbidity and mortality worldwide. Coronary heart disease and hypertension are the two major risk factors for the development of heart failure. Myocardial fibrosis, which is characteristic of all types of pathological hypertrophy, can lead to mechanical stiffness and thus contribute to contractile dysfunction.<sup>3</sup> Myocardial fibrosis leads to the loss of normal cardiac function and is closely associated with heart failure.<sup>4</sup> Acute myocardial infarction (AMI) caused by coronary artery occlusion is a major cause of morbidity and mor-

tality in humans. The loss of blood flow to myocardium results in cardiac myocyte death and myocardial remodeling. Cardiac remodeling after AMI can induce myocardial fibrosis and reduce left ventricular contractility and ultimately cause heart failure.<sup>5</sup> Modern treatment of AMI with pharmacological or mechanical reperfusion has improved survival of AMI patients. However, heart failure prevalence increases due to myocardial injury with remodeling after survival of heart attack and aging process. The failing heart is characterized by cellular and structural remodeling including cardiac myocyte hypertrophy and fibrotic deposition, which promote alterations in cardiac stiffness and function.<sup>6</sup>

Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) plays a causal role in promoting cardiac fibrosis.<sup>7-9</sup> TGF- $\beta$  may directly participate in the progressive remodeling process in heart failure. Endoglin is a 180-kDa homeodimeric membrane glycoprotein that is a co-receptor of TGF- $\beta$ 1 and  $\beta$ 3.<sup>10</sup> It is highly expressed in vascular endothelial cells and is crucial for angiogenesis.<sup>11,12</sup> Mutations in human endoglin on chromosome 9q34ter result in the autosomal dominant form of hereditary hemorrhagic telangiectasia type 1, a rare condition characterized by epistaxis

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and vascular malformation.<sup>13,14</sup> Endoglin homozygote mutation mice die at embryonic day 10.5 as a result of impaired cardiovascular development and extraembryonic angiogenesis,<sup>15</sup> while the endoglin heterozygote mutation mice are viable and recapitulate hereditary hemorrhagic telangiectasia type 1.<sup>16</sup> In cardiac tissues, endoglin is expressed in endothelial cells, and fibroblast, but cardiac myocytes fail to demonstrate significant endoglin expression.<sup>17,18</sup> Valeria et al. demonstrated that endoglin was expressed in fetal but not adult cardiac myocytes.<sup>19</sup> The extracellular domain of endoglin can be proteolytically cleaved by matrix metalloproteinase-14 and circulates as soluble endoglin (sEng).<sup>20</sup> Soluble endoglin could antagonize TGF- $\beta$ 1 signaling.<sup>18</sup>

Endoglin is a potent mediator of the profibrotic effects of angiotensin II on cardiac fibroblasts and can modulate the effect of TGF- $\beta$ 1 on extracellular matrix synthesis.<sup>21,22</sup> Endoglin is upregulated in patients with renal and liver fibrosis.<sup>23</sup> Endoglin has been shown to counteract the fibrogenic effect of TGF- $\beta$ 1 in renal interstitial fibrosis.<sup>24</sup> These data indicate that endoglin plays an important role in fibrogenesis in cardiac remodeling. This review will summarize the molecular mechanism of endoglin in profibrogenic action, myocardial fibrosis and endoglin in animal model and clinical studies.

## ENDOGLIN MODULATES PROFIBROGENIC ACTIONS OF Ang II AND TGF- $\beta$ 1

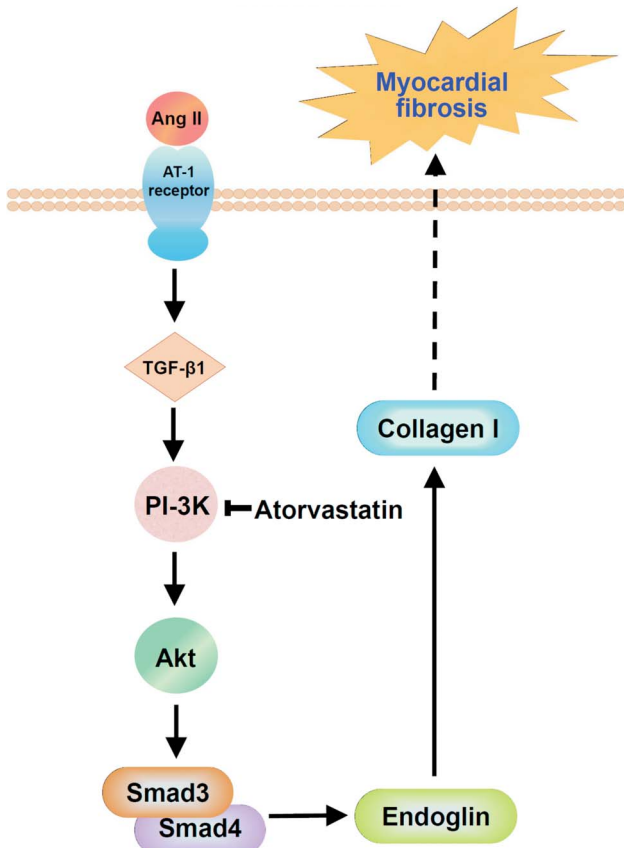
Angiotensin II (Ang II) is a pivotal mediator of myocardial fibrosis because it modulates cardiac remodeling by causing cardiac myocyte hypertrophy and myocardial fibrosis.<sup>25-27</sup> Ang II also upregulates expression of TGF- $\beta$ 1 to produce myocardial fibrosis.<sup>28</sup> Ang II and TGF- $\beta$ 1 increase cardiac fibroblast migration, proliferation and collagen production, the major pathophysiology of cardiac fibrosis.<sup>29</sup> Chen et al. found that endoglin expression in cardiac fibroblasts was upregulated by Ang II.<sup>21</sup> Ang II increased expression of endoglin mRNA and protein in a concentration and time-dependent manner.<sup>21</sup> Ang II modulated endoglin expression via Ang II type 1 receptor because angiotensin type 1 receptor blockers abrogated Ang II-induced expression of both endoglin mRNA and protein, while the angiotensin type 2 receptor blocker had no effect. Ang II increased endoglin expression

through mitogen-activated protein kinase (MAPK)p42/44 pathway. Ang II increased type 1 collagen protein expression and decreased matrix metalloproteinase-1, the collagen degrading enzyme and expression. Both effects were antagonized by a specific endoglin antibody, indicating that endoglin modulates collagen metabolism by Ang II.<sup>21</sup>

Endoglin mRNA and protein expression was significantly induced by TGF- $\beta$ 1 in cardiac fibroblasts.<sup>30</sup> Collagen I protein was also significantly induced by TGF- $\beta$ 1. Atorvastatin has been shown to reduce endoglin expression in endothelium in apo-E deficient mice and C57BL/6J mice.<sup>31,32</sup> Atorvastatin, a 3-hydroxy 3-methyl glutaryl-CoA reductase inhibitor, almost completely inhibited the endoglin and collagen I formation and protein expression induced by TGF- $\beta$ 1. Endoglin siRNA almost completely attenuated the collagen I protein expression induced by TGF- $\beta$ 1. TGF- $\beta$ 1 induced endoglin expression in cultured cardiac fibroblasts through PI-3 kinase, Akt, and Smad3 pathways. Atorvastatin attenuated the endoglin expression induced by TGF- $\beta$ 1.<sup>30</sup> This finding implies that endoglin acts as a fibrogenic mediator of TGF- $\beta$ 1 on cardiac fibroblast. The interplay between TGF- $\beta$ 1 and endoglin in cardiac fibroblast is shown in Figure 1. Cardiac myocytes responded to increased mechanical load and hormonal stimulation by hypertrophic growth.<sup>33</sup> Mechanical stretch significantly increased endoglin and collagen 1 expression in rat cardiac myoblasts.<sup>34</sup> TGF- $\beta$ 1 and overexpression of microRNA-208a (miR-208a) upregulated endoglin and collagen expression in cardiac myoblasts. Mechanical stretch increased TGF- $\beta$ 1 secretion from cardiac myocytes.<sup>35</sup> TGF- $\beta$ 1 mediates the expression of miR-208a by mechanical stretch. The interplay between mechanical stretch, TGF- $\beta$ 1, and miR-208a is shown in Figure 2. Endoglin induced by TGF- $\beta$ 1 is largely through PI-3 kinase, Akt, Smad3/4 and endoglin promoter pathways. The reduced endoglin expression resulted in less collagen I formation and less protein synthesis in cardiac fibroblasts, indicating a potential role of endoglin in cardiac remodeling.

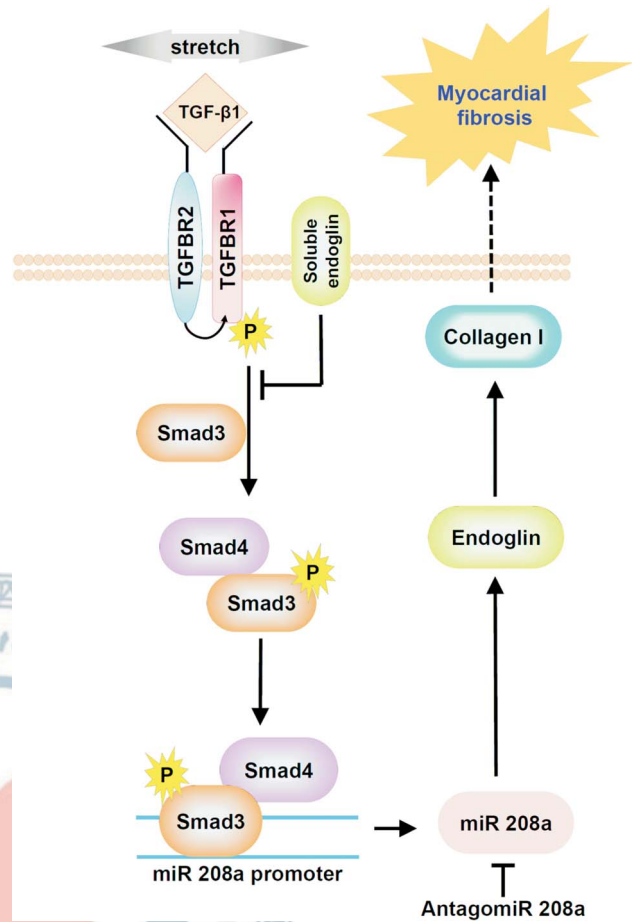
## REDUCED ENDOGLIN ACTIVITY LIMITS CARDIAC FIBROSIS IN PRESSURE OVERLOAD MODEL

The pressure overload causes concentric cardiac hypertrophy and heart failure. Transaortic constriction or



**Figure 1.** The interplay of TGF-β1 and endoglin to induce cardiac fibrosis in cardiac fibroblast. Angiotensin II (Ang II) increases TGF-β1 expression through AT1 receptor. The increased TGF-β1 activates endoglin expression through PI-3 kinase, Akt, and Smad3/4. The increased endoglin increases collagen I to induce myocardial fibrosis. Atorvastatin could inhibit PI-3 kinase phosphorylation and then reduced endoglin expression to improve myocardial fibrosis.

aortic banding is typically used in mice or rat as pressure overload model. In the animal model of pressure overload induced by transaortic constriction, left ventricular endoglin mRNA was increased within 2 weeks and remained elevated at 4 and 10 weeks.<sup>21</sup> Compared with wild type mice, left ventricular (LV) endoglin was lower in *Eng*<sup>+/-</sup> mice (endoglin-heterozygous mice). *Eng*<sup>+/-</sup> demonstrated preserved cardiac function and improved survival compared with wild type after transaortic constriction. Transaortic constriction induced LV hypertrophy or cardiac myocyte hypertrophy and was similar in *Eng*<sup>+/-</sup> and wild type mice. However, myocardial capillarility is enhanced in *Eng*<sup>+/-</sup> mice compared with wild type mice. Type 1 collagen mRNA and protein expression was significantly increased after transaortic constriction in wild type mice. Collagen expression was lower



**Figure 2.** The interplay between mechanical stretch, TGF-β1, and miR-208a in cardiac myoblasts. Mechanical stretch increases TGF-β1 secretion and then TGF-β1 increases smad3/4 phosphorylation to increase miR208a promoter activity. The increased miR208a activates endoglin and collagen I expression to induce myocardial fibrosis. The endoglin promoter sequences have specific sites that are complementary to miR-208a. Soluble endoglin could antagonize TGF-β1 signaling. Antagomir 208a could antagonize miR208a and then reduce endoglin expression to improve myocardial fibrosis.

in heterozygous mice compared with wild type mice. Silencing endoglin expression by siRNA or endoglin antibody significantly decreased type 1 collagen mRNA and protein expression in cardiac fibroblasts. sEng significantly attenuated cardiac fibrosis and type 1 collagen expression in transaortic constriction-induced heart failure.

### ENDOGLIN AND MYOCARDIAL FIBROSIS IN VOLUME OVERLOAD MODEL

Aorta-caval (AV) shunt model increased heart weight,



heart weight/body weight ratio, and increased left ventricular size without increased septal and posterior wall thickness, indicating an eccentric hypertrophy which is consistent with volume overload heart failure status. AV shunt significantly increased myocardial endoglin protein expression and cardiac hypertrophic markers such as  $\beta$ MHC and BNP.<sup>36</sup> Overexpression of miR-208a in the sham group without AV shunt significantly increased endoglin expression similar to the AV shunt group. Antagomir208a significantly attenuated the increase of myocardial endoglin and  $\beta$ MHC protein expression induced by AV shunt. Antagomir208a and pretreatment with atorvastatin in the AV shunt group significantly decreased myocardial fibrosis area induced by AV shunt. Over-expression of mutant type miR-208a in the AV shunt did not decrease the fibrosis area induced by AV shunt. The increased endoglin to induce myocardial fibrosis induced by AV shunt was mediated by miR-208a. Endoglin expression is elevated in acute volume-overload heart induced by AV shunt, indicating that endoglin plays a crucial role in pressure- and volume-overload heart failure. A miR is a small, 22-nucleotide non-protein-coding RNA that usually inhibits transcription or translation by interacting with the 3' untranslated regions of target mRNA and promoting target mRNA degradation (gene silencing).<sup>37</sup> However, Place et al. have demonstrated miR functioning to induce gene expression, not gene silencing.<sup>38</sup> MiR induces gene expression by targeting specific sites in gene promoters.<sup>38</sup> The endoglin promoter sequences have specific sites that are complementary to miR-208a.<sup>30</sup> Figure 3 summarizes the relationship of miR-208a and endoglin in myocardial fibrosis in volume-overload heart failure model.

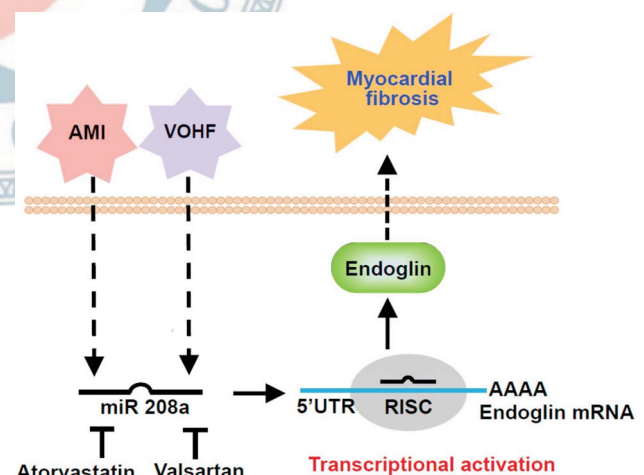
### ENDOGLIN AND MYOCARDIAL FIBROSIS IN A MOUSE MODEL OF RIGHT VENTRICULAR PRESSURE OVERLOAD

Pulmonary artery constriction causes right ventricular pressure overload and subsequently induces right heart failure. Kapur et al. demonstrated that endoglin promoted TGF- $\beta$ 1-mediated calcineurin expression and myofibroblast conversion in right ventricular fibroblasts.<sup>39</sup> Reduced endoglin expression in *Eng*<sup>+/-</sup> mice preserved indices of right ventricular diastolic function, limited

right ventricular collagen accumulation, and limited myofibroblast transformation in the right ventricle in a model of angio-obliterative pulmonary hypertension induced by exposure to hypoxia and the anti-vascular endothelial growth factor compound, Sugen as compared to wild type mice. Reduced endoglin expression in *Eng*<sup>+/-</sup> mice also preserved right ventricle function and improved survival in surgical constriction of pulmonary artery as compared to wild type mice. Right ventricle pressure overload increased right ventricle fibrosis in wild type mice, but not in *Eng*<sup>+/-</sup> mice. Treatment with neutralizing endoglin antibody improved survival of mice with severe right ventricle overload as compared to treatment with IgG control. Right ventricular fibrosis was increased in wild type mice treated with IgG control, but not in mice treated with neutralizing endoglin antibody after severe right ventricular pressure overload. The animal study by Kapur et al. supports that blocking endoglin activity reverses established right ventricular fibrosis in chronic right ventricular pressure overload in mice.<sup>39</sup>

### ENDOGLIN AND MYOCARDIAL FIBROSIS IN RAT MODEL OF ACUTE MYOCARDIAL INFARCTION

Rat model of acute myocardial infarction by ligating



**Figure 3.** Proposed pathway of acute myocardial infarction (AMI) and volume overload heart failure (VOHF) model to induce myocardial fibrosis. AMI and VOHF could increase miR-208a expression and then activate endoglin expression to induce myocardial fibrosis. Atorvastatin and valsartan could attenuate miR-208a expression and the attenuated miR-208a reduces endoglin expression and finally improves myocardial fibrosis.

the left anterior descending artery at 7 days significantly increased myocardial endoglin and  $\beta$ -myosin heavy chain protein expression and over-expression of antagomir208a significantly inhibited the increase of myocardial endoglin and  $\beta$ -myosin heavy chain protein expression induced by myocardial infarction.<sup>40</sup> Overexpression of antagomir208a and pretreatment of atorvastatin and valsartan in the AMI group significantly decreased the myocardial fibrosis area induced by myocardial infarction. Over-expression of miR-208a in the sham group without myocardial infarction significantly increased myocardial endoglin expression. Over-expression of antagomir208a in the myocardial infarction group significantly decreased the myocardial fibrosis area induced by myocardial infarction, indicating that miR-208a plays a crucial role in myocardial fibrosis after myocardial infarction. The increased endoglin to induce myocardial fibrosis induced by myocardial infarction was mediated by miR-208a, indicating endoglin is a downstream target of miR-208a in AMI. Hypoxia at 2.5% oxygen or overexpression of miR-208a alone without hypoxia for 2 h significantly increased endoglin promoter activity. This result indicates that endoglin expression is induced at the transcriptional level by miR-208a. When the miR-208a binding sites were mutated, the increased promoter activity induced by endoglin was abolished. The myocardial fibrosis and left ventricular dimension induced by AMI could be attenuated by endoglin siRNA and epigallocatechin-3-O-gallate.<sup>41</sup> Figure 3 summarizes the relationship of miR-208a and endoglin in myocardial fibrosis in AMI model.

Tseliou et al. reported that cardiospheres reduced myocardial scar and collagen mass in chronic rat myocardial infarction by inhibition of TGF- $\beta$ 1 signaling and increased soluble endoglin.<sup>42</sup> Soluble endoglin inhibits TGF- $\beta$ 1-induced cardiac fibrosis.<sup>18</sup> Cardiospheres reduced phosphorylation of smad2/3, smad4 and TGF- $\beta$  receptor 1 and TGF- $\beta$  receptor 2 expression. Soluble endoglin downregulates TGF- $\beta$ 1/smads pathway to attenuated collagen production.

## ENDOGLIN IN CLINICAL STUDIES

Endoglin expression is increased in human hearts with severe left ventricular systolic dysfunction. Endo-

glin was detected in the left ventricle in patients with end-stage heart failure for surgical implantation of a left ventricle assist device (LVAD). Endoglin expression was increased in the failing left ventricle at the time of LVAD, and returned back to control levels after LVAD support.<sup>21</sup> Endoglin has been used as a noninvasive measure of left ventricular filling pressure in heart failure<sup>43</sup> and has been regarded as a novel biomarker for acute heart failure.<sup>44</sup> Circulating levels of sEng were elevated in patients with left ventricular dysfunction. Soluble endoglin levels also decreased in association with reduced cardiac filling pressure after diuresis. Ikemoto et al. also found that plasma endoglin could be a marker to predict cardiovascular event in patients with chronic coronary artery disease after percutaneous coronary intervention.<sup>45</sup> The highest endoglin group patients had a significantly higher major adverse cardiovascular events (congestive heart failure, acute myocardial infarction, stroke, and sudden cardiac death) rate than the lowest endoglin group patients.

## CONCLUSIONS

Control of myocardial fibrosis is essential to improving myocardial performance and preventing progressive deterioration of heart failure. Endoglin plays a crucial role in myocardial fibrosis in different models of heart failure. Therefore, targeting endoglin to prevent fibrosis and heart failure may become an important and novel therapeutic strategy to improve clinical outcome in patients with heart failure in addition to the current clinical benefits of  $\beta$ -adrenergic receptor antagonists, angiotensin-converting enzyme or receptor blockers and aldosterone antagonists.<sup>46</sup>

## CONFLICT OF INTERESTS

None to declare.

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