One Step Forward for Serelaxin as a Promising Therapy in Cardiac Fibrosis

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Cardiac fibrosis is a pathological feature common to several forms of heart disease such as myocardial infarction, cardiac arrhythmias, cardiomyopathies, and heart failure. It is characterized by the net accumulation of extracellular matrix and structural remodeling of the myocardium after myocyte death, inflammation, hypertrophy, or increased workload. Several hormones, cytokines, and growth factors activate fibroblast differentiation to myofibroblasts, which produce an excessive amount of collagens in synergic response to locally produced mediators, such as transforming growth factor (TGF)-β and angiotensin II (Ang-II).

Despite the importance of cardiac fibrosis, there are currently few effective treatments to stop its progression, one of which is targeting the renin–angiotensin–aldosterone system.1 The slow progress in developing new antifibrotic therapies is attributable both to a limited understanding of the exact pathophysiological mechanism and to the nonspecific mechanisms of many antifibrotic strategies.

Relaxin was discovered in 1926 and is well known as a hormone of human reproduction. It regulates hemodynamic and renal adaptation during pregnancy and acts on the pregnant female reproductive tract inducing connective tissue remodeling to facilitate birth. Relaxin is a polypeptide family including 7 members. Serelaxin is the recombinant form of human relaxin-2. It binds to the relaxin family peptide receptor 1 activating the Gαq subunit of G protein–coupled receptors and adenylyl cyclase, thus increasing cyclic adenosine monophosphate. Other signaling mechanisms as activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 or phosphoinositide 3-kinase–Akt pathway have also been described. In the past 2 decades, relaxin has been the focus of intensive research because new studies revealed the pleiotropic actions of this mediator. In the cardiovascular system, relaxin expression has been found in heart and blood vessels of rodents and humans, and it is now considered as an autocrine or paracrine factor both in the vasculature and in the heart.2

One of the most consistent effects of relaxin is its antifibrotic activity. Treatment with relaxin or relaxin gene delivery by viral constructs inhibits development or reverses established cardiac fibrosis in different experimental models of hypertension, isoproterenol-induced cardiac injury, diabetic cardiomyopathy, transgenic cardiomyopathy, and myocardial infarction.2 Moreover, the Relaxin in Acute Heart Failure (RELAX-AHF) phase III study showed that serelaxin reduces cardiac, renal, and liver damage, as well as persistent congestion during the first few days after admission, and that these beneficial effects might be associated with increased survival.3 Despite this evidence for serelaxin as a promising treatment of cardiac fibrosis, there is a lack of head-to-head comparison with other currently available therapies.

In this context, this issue of Hypertension features an interesting study that compares the antifibrotic efficacy of serelaxin with that of enalapril.4 In a murine model of cardiac fibrosis induced by isoproterenol (daily administration for 5 days allowing cardiac fibrosis to develop for 12 additional days), serelaxin prevented left ventricular collagen concentration, and interstitial collagen staining increases to a greater extent compared with enalapril alone without modifying blood pressure. This effect was mediated by reduction of both TGF-β1 and pSmad2 levels, which was significantly higher in the serelaxin group. In fact, the antifibrotic effect of serelaxin is mediated to a large extent by inhibition of TGF-β1, which plays a fundamental role in cardiac fibrotic remodeling.5 TGF-β1 interaction with its receptor, TGFβRII, leads to Smad2 and Smad3 phosphorylation. These form homomeric and heteromeric complexes with Smad4, which translocate to the nucleus and activate the profibrogenic program, inducing myofibroblast differentiation and collagen synthesis. The balance between collagen formation and degradation is mediated by matrix metalloproteinases (MMPs) and their tissue inhibitors of metalloproteinases.

A likely mechanism for the antifibrotic action of serelaxin is the increase of nitric oxide by neuronal nitric oxide synthase activation through proline-rich receptor-like protein kinase 1/2 in myofibroblasts6 or through the suppression of the TGF-β1/pSmad2 axis, which inhibits inducible nitric oxide synthase activity in myofibroblasts7 (Figure). Although nitric oxide increase specifically contributes to MMP upregulation, the present study4 only shows a modest increase of MMP-13, but not of MMP-2, with no differences between serelaxin, enalapril, or combination treatment. There is, however, no information about tissue inhibitor of metalloproteinase levels in the different groups, which would have been helpful to further conclude on the efficacy of these treatments on MMP/tissue inhibitor of metalloproteinase activity.

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The evaluation of the antifibrotic efficacy of a combination therapy with enalapril is well based on previous findings. Local activation of the renin–angiotensin–aldosterone system contributes to the release of TGF-β1, and the antifibrotic effects of angiotensin-converting enzyme inhibitor are well recognized. Moreover, relaxin has been shown to modulate Ang-II profibrotic effects.\(^6\) In the present study,\(^4\) however, the combination of serelaxin plus enalapril showed no added benefit because it prevented fibrosis to a similar extent than serelaxin alone. A possible explanation for the lack of synergy of the combination is that the profibrotic effect of Ang-II occurs through TGF-β1 upregulation after Ang-II type 1 receptor stimulation (Figure). Serelaxin acts at TGF-β1 expression or signaling, which is where both Ang-II and TGF-β1 pathways converge. Indeed, results in cardiac fibroblasts in culture show that serelaxin significantly inhibits both Ang-II– and TGF-β1–induced effects on collagen secretion to a similar extent.\(^5\) Therefore, the present study suggests that serelaxin alone might be a better alternative than enalapril to prevent cardiac fibrosis in nonhypertensives.

When treatment was delayed, regression of isoproterenol-induced fibrosis was significantly ameliorated with serelaxin plus enalapril, whereas enalapril alone had no effect. This is the first evidence of the efficacy of serelaxin plus enalapril in reducing fibrosis progression. Moreover, both treatments significantly reduced blood pressure, suggesting that the combination therapy might be more effective in treating hypertension-related fibrosis while retaining blood pressure–lowering effects of enalapril. An important drawback in the study is that information about the effect of serelaxin alone on fibrosis regression is lacking. Unfortunately, this does not allow concluding whether the efficacy of the combination therapy is really greater than that of serelaxin alone, thus being also useful in the treatment of cardiac fibrosis in nonhypertensives.

In conclusion, the study by Samuel et al\(^4\) provides new insights and perspective into the use of serelaxin in the treatment of cardiac fibrosis. Additional studies comparing serelaxin efficacy in other animal models of cardiac fibrosis are warranted to confirm the antifibrotic efficacy of serelaxin compared with angiotensin-converting enzyme inhibitor and the beneficial added value of the combination with angiotensin-converting enzyme inhibitor. Head-to-head comparisons with other well-established antifibrotic drugs, such as aldosterone antagonists, will deserve future investigation.

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**Disclosures**

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**References**

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