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New Targets for Renal Interstitial Fibrosis: Relaxin Family Peptide Receptor 1 - Angiotensin Type 2 Receptor Heterodimers

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Abstract

Recent findings have shown that relaxin has potent anti-fibrotic effects within the kidney; however, the signal transduction mechanisms involved in the renoprotective effects of relaxin are not well understood. Chow *et al* demonstrate that the relaxin receptor, RXFP1, forms heterodimer complexes with the angiotensin type 2 receptor, AT_2, even in the absence of ligand and that these heterodimer complexes are required for relaxin's antifibrotic effects. These findings identify a previously unknown link between relaxin and angiotensin II signaling that could be a potential new target for slowing the progression of fibrotic renal diseases.

Relaxin is a small peptide in the insulin family that has been well characterized for its role in pregnancy, and recent studies have examined the beneficial effects of this hormone in cardiovascular and fibrotic diseases (1). Indeed, results of a phase III clinical trial demonstrated that Serelaxin (recombinant human relaxin -2) treatment improves symptoms and 180-day survival in patients treated for acute heart failure (2). In addition to the vasodilatory effects of relaxin, the hormone also has potent anti-fibrotic effects in experimental models of renal disease (3); however, the signaling mechanisms involved in the protective effects of relaxin have not yet been completely identified.

The renoprotective effects of relaxin have been demonstrated in various experimental models. Deletion of the relaxin gene in male mice results in renal hypertrophy dysfunction and fibrosis, and administration of exogenous relaxin to these mice *reversed* the glomerular sclerosis and tubulointerstitial fibrosis in these animals (4). In addition, relaxin treatment of aged Munich Wistar rats with established structural injury and decreased renal function *reversed* the functional decline and structural damage seen in the aging rat (5). Renal anti-fibrotic effects of relaxin have also been observed in models of renal mass reduction, angiotensin II induced hypertension, papillary necrosis, and antiglomerular basement membrane disease as recently reviewed (3). Thus, targeting the relaxin pathway may have great therapeutic potential in the treatment of fibrotic kidney diseases.

Disclosure

JMS declares no competing interests.

In this issue of *Kidney International*, Chow and colleagues (6) identify the AT_2 receptor as a critical player for the protective effects of relaxin. Although relaxin was not shown to directly interact with the AT_2 receptor itself, these investigators found that the antifibrotic effects of relaxin in both *in vivo* and *in vitro* models rely on heterodimerization of the RXFP-1 and AT_2 receptors. Previous studies by this group have provided insights into the signaling pathways through which relaxin exerts its anti-fibrotic effects within the kidney, and these findings have linked relaxin with two well known factors in the regulation of renal fibrosis: nitric oxide and transforming growth factor β (TGF-β). Nitric oxide is an essential factor in maintaining renal health (7), and in renal myofibroblasts, relaxin binds to the RXFP-1 receptor, activates G proteins and phosphorylates ERK1/2 to stimulate increased expression of nitric oxide synthase 1 (NOS1, neuronal NOS) (8). On the other hand, TGF-β contributes to progressive renal fibrosis and structural damage in the glomeruli, tubulointerstitium and tubules of the kidney (9), and studies have shown that relaxin, likely via a NOS 1 dependent pathway, can inhibit pro-fibrotic TGF-β signaling via reductions in Smad2 signaling (10,11).

The current study by Chow *et al* identifies a previously unknown role for the AT_2 receptor in relaxin signaling (6). By using either an AT_2 antagonist or AT_2 deficient mice, these authors demonstrated that the actions of relaxin on NO and TGFβ signaling as well as the anti-fibrotic effects of relaxin were completely lost both in vivo and in vitro when the AT_2 receptor was inhibited or absent. This finding has several implications for the understanding the actions of relaxin in disease states where the AT_2 receptor is upregulated and suggests that the abundance of AT_2 receptors can determine the efficacy of relaxin treatment. The authors also speculate that the RXFP1 – AT_2 heterodimers may also act to antagonize AT_1 receptor activation, thereby providing an additional mechanism by which activation of the relaxin pathway may be beneficial in renal disease (See Figure 5, of the subject paper of this commentary [reference 6] Page XX this issue.). Improved understanding of the interactions between relaxin, the AT_2 receptors and the classical renin angiotensin system in the setting of renal fibrosis will help to define the therapeutic potential of the relaxin pathway in chronic kidney disease.

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References

1. Sherwood OD. Relaxin's physiological roles and other diverse actions. Endocr Rev. 2004; 25:205–234. [PubMed: 15082520]
2. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M. RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013; 81:29–39. [PubMed: 23141816]
3. Sasser JM. The emerging role of relaxin as a novel therapeutic pathway in the treatment of chronic kidney disease. Am J Physiol Regul Integr Comp Physiol. 2013; 305(6):R559–R565. [PubMed: 23883673]

4. Samuel CS, Zhao C, Bathgate RA, DU XJ, Summers RJ, Amento EP, Walker LL, McBurnie M, Zhao L, Tregear GW. The relaxin gene-knockout mouse: A model of progressive fibrosis. Ann N Y Acad Sci. 2005; 1041:173–181. [PubMed: 15956703]

5. Danielson LA, Welford A, Harris A. Relaxin improves renal function and histology in aging Munich Wistar rats. J Am Soc Nephrol. 2006; 17:1325–1333. [PubMed: 16597680]

6. Chow BSM, Kocan M, Bosnyak S, Sarwar M, Wigg B, Jones ES, Widdop RE, Summers RJ, Bathgate RAD, Hewitson TD, Samuel CS. Relaxin inherently requires the angiotensin II trype 2 (AT2) receptor to abrogate renal interstitial fibrosis. Kidney International. In Press.

7. Baylis C. Nitric oxide deficiency in chronic kidney disease. Am J Physiol Renal Physiol. 2008; 294:F1–F9. [PubMed: 17928410]

8. Chow BS, Chew EG, Zhao C, Bathgate RA, Hewitson TD, Samuel CS. Relaxin signals through a RXFP1-pERK-nNOS-NO-cGMP-dependent pathway to up-regulate matrix metalloproteinases: the additional involvement of iNOS. PLos One. 2012; 7:e42714. [PubMed: 22936987]

9. López-Hernández FJ, López-Novoa JM. Role of TGF-β in chronic kidney disease: an integration of tubular, glomerular and vascular effects. Cell Tissue Res. 2012; 347:141–154. [PubMed: 22105921]

10. Heeg MH, Koziolek MJ, Vasko R, Schaefer L, Sharma K, Muller GA, Strutz F. The antifibrotic effects of relaxin in human renal fibroblasts are mediated in part by inhibition of the Smad2 pathway. Kidney Int. 2005; 68:96–109. [PubMed: 15954899]

11. Mookerjee I, Hewitson TD, Halls ML, Summers RJ, Mathai ML, Bathgate RA, Tregear GW, Samuel CS. Relaxin inhibits renal myofibroblast differentiation via RXFP1, the nitric oxide pathway, and Smad2. FASEB J. 2009; 23:1219–1229. [PubMed: 19073841]