Relaxin: Exploring the antifibrotic potential of a pregnancy hormone

Excess accumulation of extracellular matrix proteins has been well recognized as a key feature of chronic kidney diseases. Renal fibrosis, particularly tubulointerstitial fibrosis, parallels the progressive loss of organ function, which ultimately leads to overt renal failure and the need for dialysis. Driven by distinct causes like hypertension, chronic inflammation, elevated blood glucose, or postrenal obstruction, development of kidney fibrosis is mediated and fine-tuned by a variety of cytokines, growth factors, and soluble factors. Among others, transforming growth factor-beta (TGF-β) is of pivotal importance because of its ability to regulate both matrix protein synthesis and degradation in a distinctive profibrotic manner. As the knowledge about TGF-β and matrix protein biology and pathophysiology has substantially increased over the recent years, new strategies to tackle renal fibrosis have been developed that are centered around the cascade of TGF-β generation, TGF-β signaling, and matrix protein deposition and degradation.

An emerging novel therapeutic approach to target fibrosis is relaxin, a small peptide hormone that is endogenously produced by corpus luteum of the ovary. The name relaxin is derived from its unique ability to soften connective tissue of the reproductive tract in pregnancy (i.e., to relax the cervix and the pubic ligament to facilitate delivery) [1]. Relaxin has received additional interest because it mediates the profound vascular effects seen in pregnancy, too. The general hemodynamic changes and, especially, the changes in renal hemodynamics in pregnancy (decline in renal vascular resistance, increase in renal plasma flow and GFR) are mediated in large parts by relaxin through actions on nitric oxide and endothelin receptor B activation [1, 2]. Of particular interest to nephrologists, relaxin blocks the renal hemodynamic effects of angiotensin II independently of pregnancy [3]. These vascular effects appear largely dependent on the activation of matrix-metalloproteases (MMP), enzymes that digest and remove collagens and other matrix proteins [1, 2, 4]. Activation of MMPs by relaxin has been demonstrated in a large variety of cell types in vitro. Studies from relaxin knock-out mice have shown a marked age-dependent fibrosis in nonreproductive organs such as the kidney, heart, and lung [4, 5]. Administration of recombinant relaxin has been documented to substantially reduce matrix accumulation in models of pulmonary and liver fibrosis [1, 6]. In renal models, antifibrotic and function-preserving effects of recombinant relaxin were of a comparable magnitude as seen with ACE inhibition [7]. In 12-month-old male relaxin knock-out mice, a short-term relaxin treatment largely reduced chronic renal collagen build-up, indicating regression of established renal fibrosis [5]. Together, these studies show a clear inhibitory effect of relaxin on tissue fibrosis, expanding its role from a mere hemodynamic agent to an important negative regulator of tissue matrix protein content.

The study presented in this issue of Kidney International by Heeg et al [8] elegantly expands our current knowledge of relaxin actions on renal matrix protein accumulation. Using human kidney fibroblasts, the authors show that relaxin blocks TGF-β effects on matrix synthesis and secretion, as well as the transformation of fibroblasts to myofibroblasts. Following a recurring theme in relaxin biology, the secretion of matrix degrading enzymes (MMP-2 and MMP-9) was induced as well in human renal fibroblasts. Interestingly, the authors were able to show that relaxin blocks the activation of Smad2, a pivotal messenger of TGF-β effects, thus providing additional mechanistic data on relaxin effect on TGF-β that go beyond MMPs. The use of well-characterized human renal cell lines in this study provides encouraging evidence that a lot of the beneficial effects of relaxin on TGF-β and matrix protein biology are not only operative in rodent disease models, but also in human cells. It clearly adds to the recently published papers that provide exciting and challenging new data on relaxin biology.

Recently, tissue binding sites for relaxin were identified as the previous orphan leucine-rich guanine nucleotide-binding receptors 7 and 8 (LGR-7 and LGR-8) [1, 2, 4]. LGR-7 is expressed in renal cells, and this raises the question of a possible regulated expression in renal cells in health and disease. Relaxin and TGF-β are potentially engaged in a more complex interaction, as a recent
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report suggests that shows a down-regulation of the relaxin receptor after TGF-β treatment in human endometrial cells [9]. H3, a new member of the relaxin gene family, has been described [4], which also engages with LGR-7. Most intriguing is the discovery of local relaxin synthesis in human tissues outside the reproductive tract. In human heart failure, there is cardiac relaxin synthesis, and plasma relaxin levels are elevated proportionally to disease severity [10]. Furthermore, relaxin is supposedly expressed by rat and mouse kidneys, although definite data have not been reported yet [2]. A lot of this work still has to be studied in more detail, and to be expanded into the field of renal disease, but the relaxin story is somewhat reminiscent of that of other molecules whose scope of action has gone from very limited roles to broad involvement in multiple organs in health and disease. Relaxin’s obvious inherent capacity to facilitate matrix protein degradation and to regress established renal fibrosis deserves our further attention and research efforts.

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REFERENCES