Relaxin: an emerging therapy for fibroproliferative disorders

Chrishan S. Samuel
Howard Florey Institute and Department of Biochemistry and Molecular Biology, The University of Melbourne, Parkville, Victoria 3010, Australia

Originally described for its ability to remodel the birth canal during pregnancy, the hormone relaxin is emerging as both an endogenous inhibitor of collagen turnover and a potential therapy for the progressive fibrosis that occurs during tissue repair and end-stage organ disease. Relaxin has now been shown to potently and rapidly inhibit fibrogenesis in diverse experimental models of dermal, cardiovascular, renal (glomerular and tubulointerstitial), pulmonary/airway and hepatic disease. In several of these models, short-term continuous infusion of relaxin is also able to reverse established fibrosis. Importantly, relaxin only inhibits pro-fibrotic cytokine (TGF-β1, angiotensin II, interleukin-1β)-stimulated collagen and fibronectin deposition in primary fibroblast culture models *in vitro* and animal models of injury/disease *in vivo* without affecting basal matrix turnover; suggesting that it is a safe therapeutic. Consistent with this, relaxin has been evaluated in a number of clinical trials and has demonstrated an excellent safety profile in humans with minimal side-effects. The anti-fibrotic actions of the hormone have been found to primarily involve the down-regulation of Smad2 phosphorylation as a means of interfering with TGF-β1 signaling and hence, the ability of TGF-β1 to promote myofibroblast differentiation and collagen production. Additionally, relaxin has been found to antagonize TGF-β1-stimulated collagen I lattice contraction, while promoting matrix metalloproteinase expression and activity, and inhibiting the actions of the tissue inhibitors of metalloproteinases to induce collagen breakdown. These combined actions along with its ability to promote vasodilation, angiogenesis and wound healing highlight its potential as a therapy for fibroproliferative disorders; which will be discussed.

This work was supported by the National Health & Medical Research Council of Australia and the National Heart Foundation of Australia.