Cardiotrophin-1 is involved in renal fibrosis development

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by a progressive decrease in glomerular filtration rate that eventually leads to renal failure. Tubulointerstitial fibrosis, a major determinant of CKD, occurs by inflammatory cell infiltration, myofibroblast activation and proliferation in the renal interstitium leading to accumulation of extracellular matrix (ECM) proteins. Cardiotrophin-1 (CT-1) is a member of the interleukin-6 (IL-6) family of cytokines, originally identified as a protein capable of inducing hypertrophy in neonatal ventricular cardiomyocytes. CT-1 has a great number of functions that sometimes have opposite effects in different contexts. It can promote cell survival but also can cause tissue damage. Chronic exposure of CT-1 is associated with cardiac, vascular and renal fibrosis, resulting in further structural and functional damage in heart, aorta, and kidney. However, acute administration of CT-1 prevented almost completely contrast-induced nephropathy. Therefore, the role of CT-1 in renal fibrosis is not clearly described.

AIM

The aim of this study is to assess the severity of renal tubule-interstitial damage induced by unilateral ureteral obstruction (UUO), an experimental model of tubulointerstitial-fibrosis, in animals lacking CT-1 and in their respective controls.

MATERIALS AND METHODS

OUU was performed in CT-1$^{-/-}$ mice and their respective controls (WT) during 3 days –in order to analyse inflammatory effects and initial tubule-interstitial damage- and during 15 days – in order to evaluate renal tubule-interstitial fibrosis. Moreover we have studied the effect of CT-1 treatment (100 µg/kg) every 2 days in WT mice. Interstitial fibrosis was evaluated by histological techniques. Myofibroblast markers (smooth muscle actin, α-SMA), inflammation markers (Intercellular Adhesion Molecule 1 -ICAM-1- and cycloxigenase-2 -COX-2), and extracellular matrix components (Collagen-1, etc) were evaluated by Western blot and qPCR. We also assessed collagen deposition in renal tissue by Sirius red staining.

RESULTS

Our results show that after 3 days of UUO, obstructed (O) kidneys from CT-1$^{-/-}$ mice showed significantly higher expression of ICAM-1 , COX-2 and collagen I but similar levels of α-SMA than O kidneys from WT mice (figure 1). After 15 days of UUO, O kidneys from CT-1$^{-/-}$ show higher expression of collagen I than O kidneys from WT (figure 2). In addition, Sirius red staining showed increased tubulointerstitial fibrosis in O kidneys from CT-1$^{-/-}$ mice than in their respective O controls (figure 3). CT-1 treatment (100 µg/kg) reduced the increased ICAM-1 expression observed after 3 days UUO (figure 4); the same treatment reduced the increases in collagen I, CTGF and the extension of Red Sirius- stained area in O kidneys after 15 days UUO (figure 5).

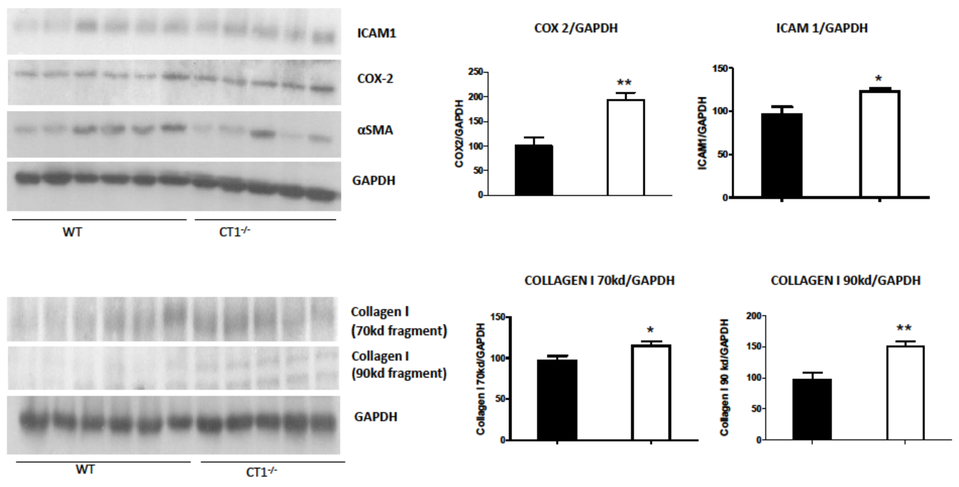

Fig 1. Analysis of ICAM-1, COX2, αSMA and collagen I in O kidneys from CT-1$^{-/-}$ and WT mice after 3 days of UUO evaluated by western blot. *P<0,05 **P<0,01

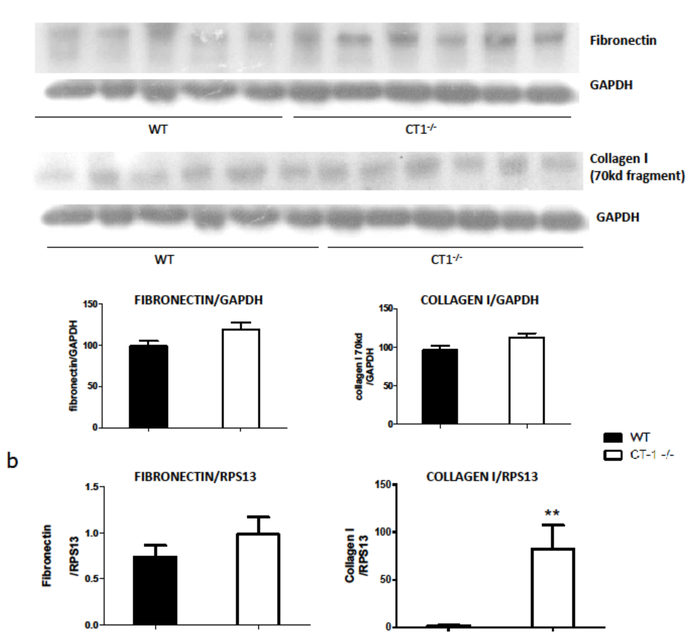

Fig 2. Analysis of fibronectin and collagen I in O kidneys from CT-1$^{-/-}$ and WT mice after 15 days of UUO evaluated by western blot (a) and by qPCR (b). *P<0,05 **P<0,01

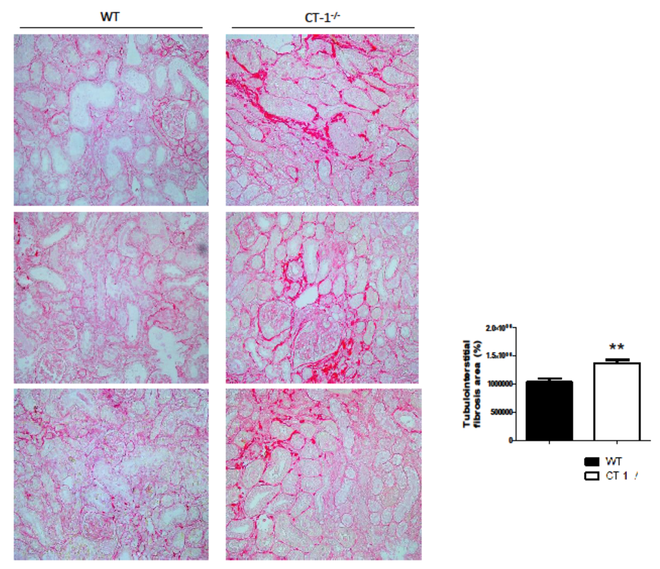

Fig3. Analysis of tubulointerstitial fibrosis area in O kidneys from CT-1$^{-/-}$ and WT mice after 15 days of UUO evaluated by sirius red staining. *P<0,05 **P<0,01

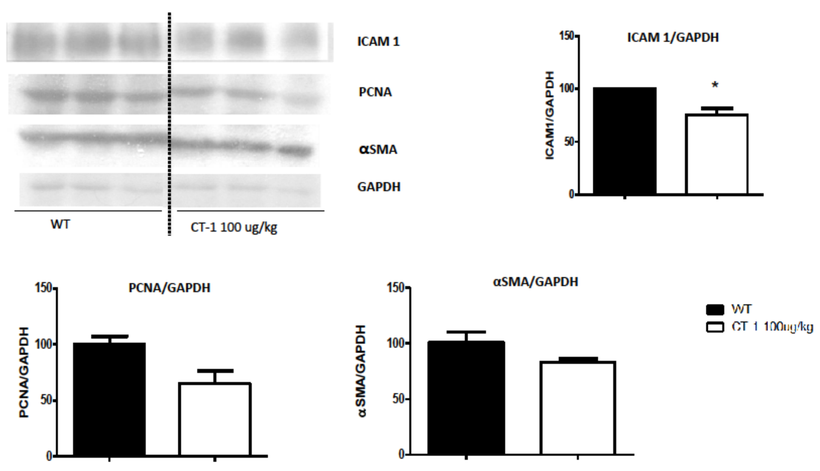

Fig 4. Analysis of ICAM-1, PCNA and αSMA in O kidneys from WT mice and WT mice treated with CT-1 100 µg/kg after 3 days of UUO, evaluated by western blot. *P<0,05 **P<0,01

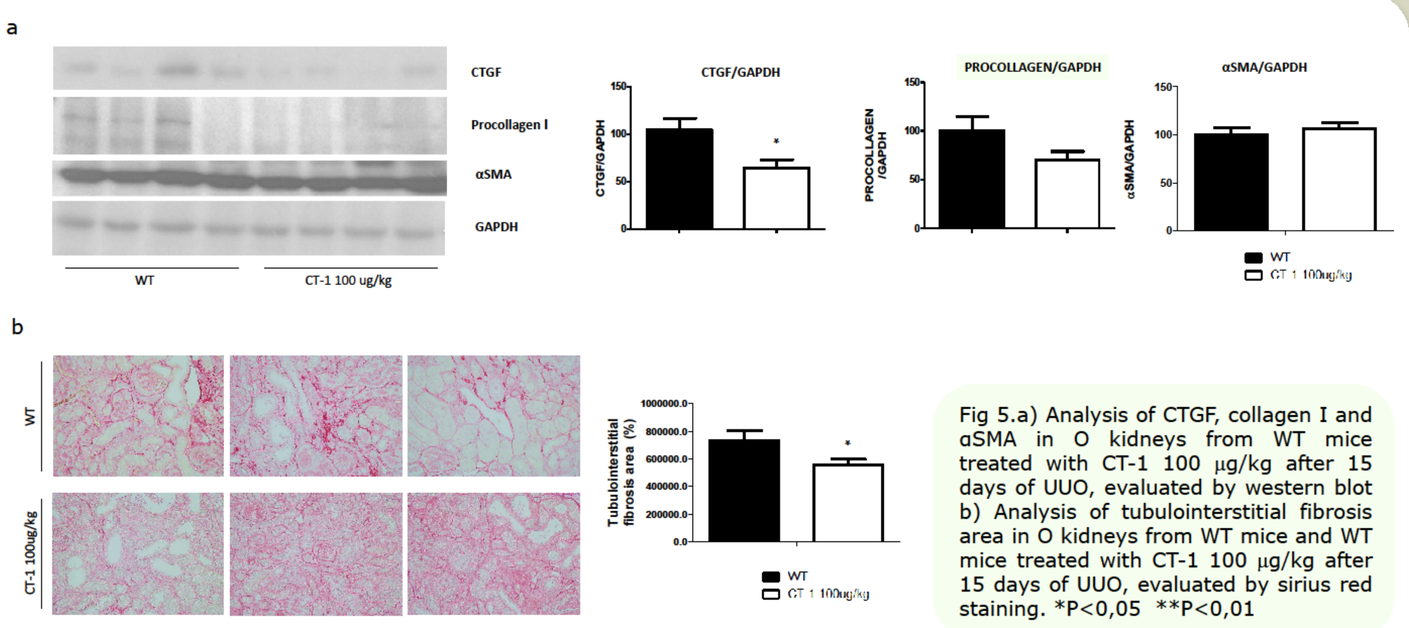

Fig 5.a) Analysis of CTGF, collagen I and αSMA in O kidneys from WT mice treated with CT-1 100 µg/kg after 15 days of UUO, evaluated by western blot b) Analysis of tubulointerstitial fibrosis area in O kidneys from WT mice and WT mice treated with CT-1 100 µg/kg after 15 days of UUO, evaluated by sirius red staining. *P<0,05 **P<0,01

CONCLUSIONS

This study shows that CT-1 regulates renal fibrosis induced by obstructive nephropathy, possible due to its regulation of the inflammatory process, thus suggesting a potential therapeutical property of this molecule.

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