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RENOPROTECTIVE EFFECTS OF CARDIOTROPHIN-1 IN A MOUSE MODEL OF
CHRONIC KIDNEY DISEASE

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The prevalence of chronic kidney diseases (CKD) is increasing worldwide with negative consequences to quality of life for the individual subjects and to national health economics.¹ CKD patients are at risk of progressing to end-stage renal disease (ESRD) with the need of life-long dialysis or kidney transplantation. Renal tubulointerstitial fibrosis is the final common pathway of CKD promoting the consecutive loss of kidney function. The histopathological hallmarks of renal fibrosis are tubular atrophy, expansion of the renal interstitium due to accumulation of extracellular matrix proteins (e.g. collagens) and loss of peritubular capillaries. The mechanisms underlying the initiation and progression of renal fibrosis are only incompletely understood but involve a complex interplay between inflammation, apoptosis and hypoxia among others in addition to recruitment and activation of matrix producing myofibroblasts. In the present issue of *Acta Physiologica*, Perretta-Tejedor *et al.* adds a new piece of evidence to the puzzle of renal fibrosis showing that cardiotrophin-1 (CT-1) has renoprotective effects in the unilateral ureteral obstruction (UUO) model of CKD² in mice suggesting CT-1 as a potential target candidate to be used for renoprotective treatment in CKD patients.

In the study, Perretta-Tejedor *et al.* investigates the role of CT-1 in CKD by the use of transgenic CT-1 mice.² CT-1 was discovered in 1995 as a new member of the IL-6 family of cytokines and was first recognized for its cardiac effects and ability to induce cardiomyocyte hypertrophy.³ CT-1 has since been associated with cytoprotective effects in various organ systems such as the central nervous system and the liver. The cytokine has also been suggested to have renoprotective effects in acute conditions such as ischemia-reperfusion injury in both transplanted⁴ and native kidneys and drug-induced nephrotoxicity⁵ but has not previously been investigated in CKD. In the present study, Perretta-Tejedor *et al.* uses the UUO model in mice with genetic deficiency of CT-1 and shows convincing data of aggravated renal damage in CT-1 deficient mice compared to wild-type litter mate

controls. Thus after 15 days of UUO, lack of CT-1 results in more severe histomorphological signs of renal damage and more extensive accumulation of extracellular matrix proteins.²

Seen from a mechanistic point of view, these experiments are supported by additional analyses in mice with 3 days of UUO showing increased apoptosis and expression of inflammatory markers in obstructed kidneys from CT-1 deficient mice. Inflammation and apoptosis are well known mediators of kidney injury, and the results published in *Acta Physiologica* by Perretta-Tejedor *et al.*² suggest CT-1 to have cytoprotective effects during CKD development through an anti-inflammatory mechanism. The current knowledge of CT-1 is predominantly obtained from rodent studies and significant knowledge would be added to the field by additional studies of CT-1 function in the human setting to reveal the translational potential of the CT-1 renoprotective effects. Thus, studies of CT-1 expression in both normal human kidney tissue and in kidney tissue from CKD patients would be of interest just as correlation studies of CT-1 and renal fibrosis scores/kidney function in CKD patients would add to the knowledge of the CT-1 potential in CKD patients.

Renal myofibroblasts are the source of extracellular matrix proteins, and development of renal fibrosis involves a significant disturbance in extracellular matrix homeostasis with the production exceeding the degradation resulting in interstitial accumulation of extracellular matrix proteins. Perretta-Tejedor *et al.* shows that CT-1 is expressed in renal fibroblasts and that endogenous deficiency leads to activation and increased matrix production² supporting a direct role of CT-1 in renal fibroblast dynamics independent of systemic inflammation. The major source of renal myofibroblasts is proliferation of resident interstitial fibroblast⁶ but currently it still remains to be established if CT-1 also plays a role in the regulation of fibroblast proliferation. The renal fibroblast is an attractive target cell for renoprotective treatment since impaired fibroblast activation and/or proliferation could prevent the detrimental matrix accumulation seen in renal fibrosis. The

role of endogenous CT-1 in renal fibroblasts unraveled by the present study can hopefully support future development of novel treatment strategies to prevent the progression of renal fibrosis.

Apart from studies of endogenous CT-1, also the effects of exogenous CT-1 were investigated by Perretta-Tejedor *et al.* Administration of exogenous CT-1 during the UUO period not only convincingly reduces the development of renal fibrosis in CT-1 deficient mice but also in wild-type mice with intact endogenous CT-1 production.² These results are of special interest since they suggest a previously unexploited treatment potential because endogenous CT-1 production is not able to fully saturate the need of the cytokine during organ protection. Currently the only known therapy that can slow down the progression of CKD to ESRD is ACE-inhibitor treatment but no targeted therapy directed against the mechanisms leading to renal fibrosis is known. One of the major reasons for this lack of treatment might be the very complex mechanistic nature of renal fibrogenesis. ESRD patients have reduced quality of life in addition to increased mortality and morbidity underlining the need of new targeted treatment strategies. The current study by Perretta-Tejedor *et al.*² suggests CT-1 to be a target of interest, and it will be interesting to follow the future development of this cytokine. The UUO model is interesting especially for screening of new proteins involved in chronic kidney damage and renal fibrosis but also has its limitations. Therefore, further studies in other CKD models such as diabetic and hypertensive nephropathy in addition to AKI-to-CKD progression will be interesting to follow.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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