Renotropic role and therapeutic potential of HGF in the kidney

Kunio Matsumoto and Toshikazu Nakamura

Division of Molecular Regenerative Medicine, Course of Advanced Medicine, Osaka University Graduate School of Medicine, Suita, Osaka 565-0871, Japan

Abstract
Hepatocyte growth factor (HGF) has mitogenic, morphogenic and anti-apoptotic activities on renal epithelial cells, and is a potential renotropin for renal regeneration. In chronic renal failure/fibrosis, HGF in the kidney declines in a manner reciprocal to the increase in transforming growth factor-β (TGF-β). Neutralization of HGF by the antibody leads to acceleration of renal failure/fibrosis, while HGF administration leads to remarkable attenuation, thus indicating the importance of the balance between HGF and TGF-β in the pathogenesis and therapy of chronic renal failure. HGF is strongly considered as potential treatment for acute and chronic renal failure.

Keywords: acute renal failure; chronic renal failure; c-Met; HGF; renal regeneration; renotropin

Introduction
Many therapies depend on the intrinsic ability of tissues to regenerate, and understanding of the mechanisms involved in tissue regeneration will make way for treatment of subjects with diseases and injuries. The kidney has the potential to regenerate following injuries and diseases. After unilateral nephrectomy, a compensatory renal enlargement occurs and the presence of a blood-borne ‘renotropin’ was deduced from laboratory data. Although renotropin has yet to be clearly identified, recent approaches indicate that hepatocyte growth factor (HGF) is closely associated with renal regeneration. HGF was identified and cloned as a mitogen for mature hepatocytes [1,2], and the receptor for HGF is the c-Met proto-oncogene product of heterodimeric tyrosine kinase (Figure 1A). HGF has mitogenic and anti-apoptotic actions on renal tubular cells, podocytes and endothelial cells [3,4]. Likewise, HGF exerts morphogenic response, e.g. induction of branching tubulogenesis in renal epithelial cells [5]. In the kidney, HGF is expressed in interstitial cells, probably endothelial cells, macrophages and mesangial cells [3,4]. Thus HGF mediates epithelial–stromal and endothelial–mesangial interactions in the kidney (Figure 1B). We here focus on the renotropic role of HGF and its therapeutic potential in the treatment of renal diseases.

Results and discussion
HGF mRNA and protein levels are induced rapidly in the remaining kidney after unilateral nephrectomy [6]. Rapid increases in HGF mRNA and protein levels in the kidney and blood were also noted in acute renal injury induced by administration of HgCl₂ and by renal ischaemia [7]. Rapid increases in HGF levels in the kidney and blood seem to reflect compensatory responses to renal injury, to prevent acute tubular death and to induce renal regeneration. Based on these results, potential application of HGF for acute renal injuries was examined in laboratory animals. Administration of recombinant HGF stimulates renal regeneration after unilateral nephrectomy, and acute renal injuries induced by administration of HgCl₂, cisplatin and tacrolimus [3,4,7–9]. Compared with control animals, rats given HGF after acute renal injury had better renal functions and much less histological damage, and mortality was reduced. Thus the onset of acute renal failure was strongly prevented by HGF [7–9]. These results suggest that HGF is a potential candidate for the ‘renotropin’ in compensatory renal enlargement and regeneration and that it may be used for treatment of patients with acute renal diseases.

Fibrotic organ diseases such as liver cirrhosis, lung fibrosis and chronic renal failure are devastating for the functions of these organs and are progressive diseases, characterized by accumulation of extracellular matrix (ECM) components and withdrawal
of parenchymal cells. The overexpression of transforming growth factor-β (TGF-β) is a key event leading to the various fibrotic disorders, including renal fibrosis. On the other hand, we demonstrated that endogenous HGF protects the nephrotic kidney from fibrosis [10–12]. In ICGN mice, glomerular injury is
detectable from 3 weeks postnatally, while renal dysfunction occurs from 3–4 months after birth and the dysfunction coincides with tubular destruction and interstitial fibrosis. At an early stage of renal injury, the ICGN mice showed increased expression of HGF and compensatory tubular proliferation. In later stages, the renal HGF level decreased markedly, coinciding with a reduction in tubular proliferation, whereas renal TGF-β expression increased remarkably in accordance with the extension of fibrosis. Expressions of TGF-β and HGF become altered in a reciprocal relationship during progression of renal fibrosis and dysfunction (Figure 1C). Importantly, neutralization of endogenous HGF by anti-HGF antibody strongly accelerated progression of renal fibrosis and dysfunction. Not only an increase in TGF-β levels, but also a decrease in renal HGF expression is responsible for the occurrence of renal fibrosis.

The therapeutic efficacy of HGF was examined in ICGN mice and a model for renal fibrosis caused by unilateral ureter obstruction [10–12]. In the case of ICGN mice, HGF was administered for 4 weeks, during middle- to end-stage chronic renal disease. In control animals, molecular and cellular events leading to end-stage chronic renal disease progressed during this period. Kidney TGF-β levels, the number of myofibroblasts, collagen accumulation and the degree of tubular apoptosis increased, whereas the number of proliferating tubular cells decreased. In contrast, in mice treated with HGF, expression of TGF-β, ECM accumulation, and the number of myofibroblasts and degree of tubular apoptosis decreased, whereas the number of regenerating tubular cells increased. Consistent with these changes, the beneficial effects of HGF on clinical outcome were indicated by lower levels of serum creatinine, blood urea nitrogen and urine albumin, and by evidence of decreased injury by renal histology. Similar therapeutic effects of HGF on renal fibrosis were seen in a unilateral ureter obstruction model [12]. These results indicate that treatment with HGF has therapeutic effects in cases of chronic renal disease (Figure 1C).

References