Reciprocal functions of hepatocyte growth factor and transforming growth factor-β1 in the progression of renal diseases: A role for CD44?

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Reciprocal functions of hepatocyte growth factor and transforming growth factor-β1 in the progression of renal diseases: A role for CD44? Progressive renal fibrosis occurs via common pathophysiologic mechanisms, regardless of the primary underlying disease. This cascade includes release of cytokines/chemokines and toxic molecules, interstitial inflammation, tubular cell damage, accumulation of myofibroblasts, and finally, fibrosis. Hepatocyte growth factor (HGF) and transforming growth factor-β1 (TGF-β1) are key molecules in this cascade that, in general, exert opposite actions. Hepatocyte growth factor promotes, to some extent, inflammation, protects tubular epithelial cells, blocks myofibroblast transition, and contributes to tissue remodeling. In contrast, TGF-β1 has powerful anti-inflammatory actions, promotes apoptosis, induces myofibroblast transition, and is a strong pro-fibrotic agent. The mechanisms which orchestrate the reciprocal actions of HGF and TGF-β1 are still largely unknown and are probably multiple. One of these mechanisms involves the selective up-regulation of CD44 in damaged kidney. The glomerular and tubular expression of CD44 closely correlates with the degree of renal damage, and CD44 has been shown to facilitate the action of both HGF and TGF-β1. Moreover, during chronic obstructive nephropathy CD44 knock-out mice display much more tubular damage but develop less fibrosis in the course of the renal disease. These histologic findings are associated with impairment of signaling pathways of both HGF and TGF-β1. The development of new therapeutic strategies aimed at preventing progression of renal diseases that are based on HGF and/or TGF-β1 may take in account the pivotal role of CD44 expression in the functions of both molecules.

The majority of progressive renal diseases are glomerular and vascular in origin, whereas the renal outcome is largely determined by the extent of secondary tubulo-interstitial damage. Irrespective of the primary insult, the histologic lesions of kidneys with chronic renal failure are remarkably similar and characterized by glomerular sclerosis and tubulointerstitial scarring. This suggests a common pathway in the development of these lesions. Experiments in animal models that mimic the complex milieu of progressive renal diseases in humans have dissected the cascade of events that lead to end-stage kidney disease. It is beyond the scope of this review to analyze in details all mechanisms that take place during progressive renal disease. Excellent reviews have addressed this topic recently [1, 2]. Here, we focus on the reciprocal roles of hepatocyte growth factor (HGF) and transforming growth factor-β1 (TGF-β1) in progression of renal disease and we examine the potential role of CD44 in the balance between these growth factors. First, the key events that take place upon renal injury are summarized in Figure 1.

The mechanisms of renal disease progression in brief

Upon injury, glomeruli release cytokines and chemokines. These inflammatory mediators, combined with other proteins, immune complexes, toxins, iron, complement factors [3] are filtered by damaged glomeruli and will stimulate downstream tubular epithelial cells (TEC) to start producing cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), and chemokines such as IL-8, monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T cell expressed and secreted (RANTES) [4]. This, in turn, leads to the up-regulation of adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and CD44 [5], which support infiltration and activation of inflammatory cells. The inflammatory infiltrate, mostly composed of monocytes/macrophages and T lymphocytes, contributes to a positive feedback of inflammation. Macrophages and their products are implicated in various deleterious processes in the course of renal damage such as direct cell toxicity, basement membrane damage, and interstitial fibrosis. On the other hand, macrophages are also involved in tissue repair by phagocytosing apoptotic bodies, removing immune complexes and fibrin, and secreting protecting mediators such as HGF [6, 7]. Progression of renal disease correlates with impaired angiogenesis, which results from an increase in the expression of the anti-
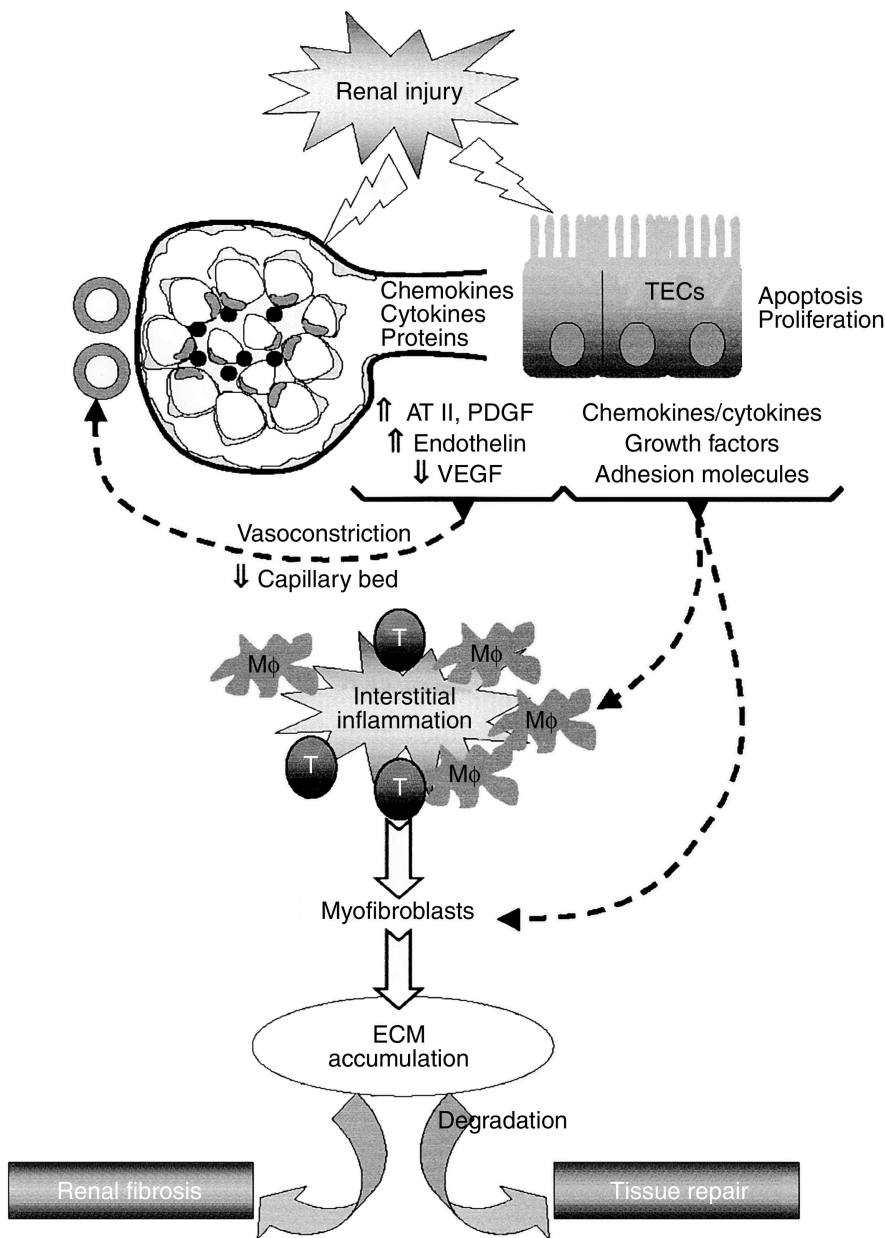
Fig. 1. Pathophysiologic mechanisms of renal damage. Abbreviations are: AT, angiotensin; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; TECs, tubular epithelial cells; T, T lymphocyte; Mϕ, macrophage; ECM, extracellular matrix.

angiogenic factor thrombospondin-1 (TSP-1), and decrease of the pro-angiogenic factor vascular endothelial growth factor (VEGF) by TEC [8, 9]. Depending on the balance between growth factors, TEC may eventually become apoptotic, start to proliferate, or undergo myofibroblast transition. The accumulation of myofibroblasts in the interstitium is a key event in the development of fibrosis. The origin of these cells is probably multiple, including TEC, interstitial fibroblasts, macrophages, and pericytes [10]. These cells are characterized by the expression of α-smooth muscle actin (α-SMA) and fibroblastic-specific protein-1 (FSP-1) [11]. Extracellular matrix (ECM) accumulation results from an imbalance

between synthesis by myofibroblasts and degradation by matrix metalloproteinases (MMP) [12]. This cascade of events is schematized in Figure 1.

The reciprocal functions of TGF-β1 and HGF in renal disease progression

In renal disease progression, TGF-β1 and HGF exert reciprocal and essential functions [13, 14], as reviewed in Figure 2. Transforming growth factor-β1 and HGF share similar cellular sources, including macrophages, TEC, and myofibroblasts [15, 16]. Numerous factors are known to stimulate TGF-β1 production, including angiotensin II, endothelin-1, ischemia, insulin, glucose, shear
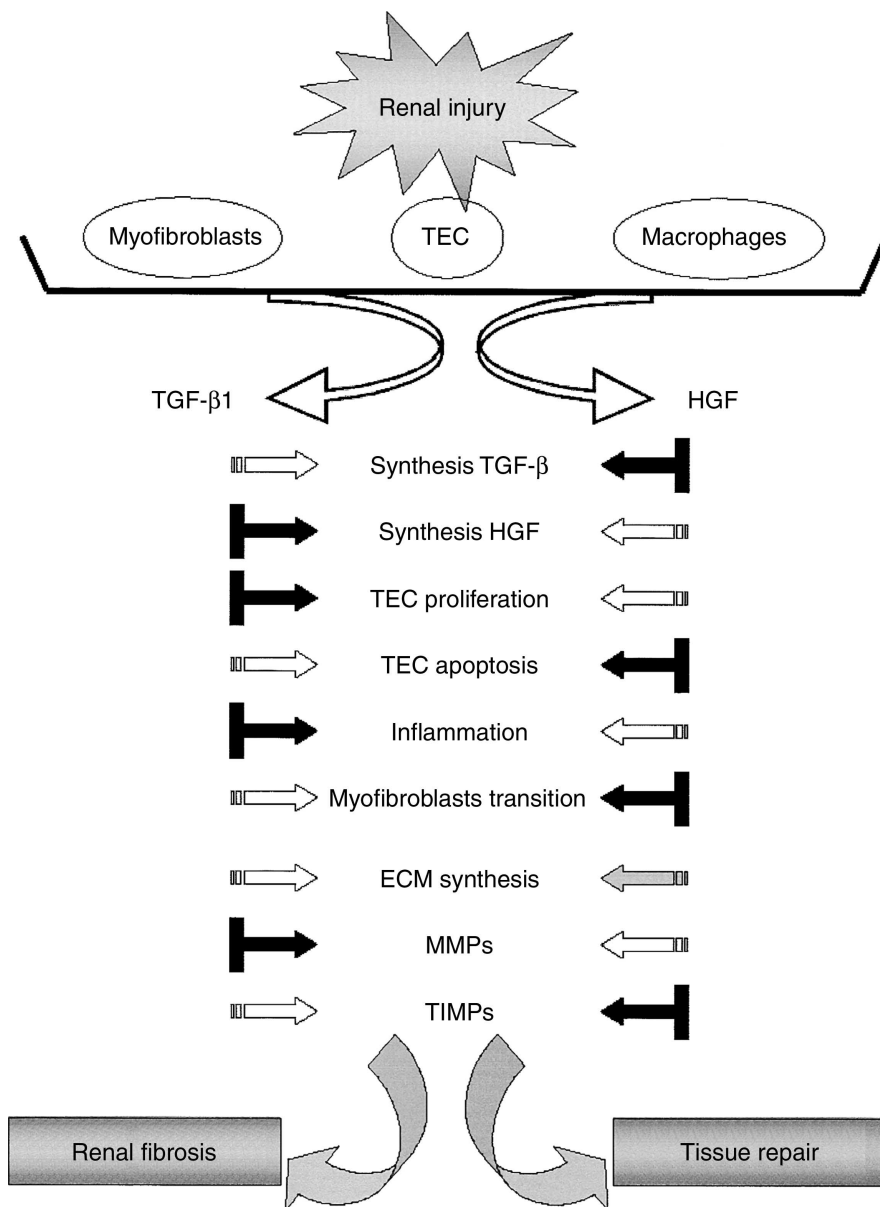
Fig. 2. The reciprocal effects of transforming growth factor-β1 (TGF-β1) and hepatocyte growth factor (HGF) in the cascade of tubulo-interstitial damage. Black arrows, inhibitory actions; gray arrows, controversial actions; open arrows, stimulatory actions. Abbreviations are: TECs, tubular epithelial cells; ECM, extracellular matrix; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of matrix metalloproteinase.

stress, insulin growth factor-1 (IGF-1), atrial natriuretic factor, platelet-activating factor, thromboxane, and TGF-β1 [2]. To become biologically active, pro-TGF-β1 must be cleaved by a proteinase such as MMP-9, thrombospondin, or plasmin [17–19]. Heparin and IL-1 are the most powerful mediators involved in the secretion of HGF [20–22]. Transforming growth factor-β1 and HGF inhibit the synthesis of each other [23] and HGF also down-regulates the expression of TGF-β receptor 1 (TGF-βR1) in vivo [24]. Experimental studies in rodent models of chronic kidney diseases revealed that HGF is produced principally at an early stage of renal damage when tubulointerstitial inflammation and proliferation of TEC dominate the picture [25, 26], and that (active)

TGF-β1 is strongly expressed at a later stage of renal damage when apoptosis of TEC and interstitial fibrosis occur [23, 27].

Transforming growth factor-β1 exerts powerful anti-inflammatory effects in organ damage [28, 29]. In contrast, the role of HGF in inflammation is still controversial. In vitro, HGF induces MCP-1 and RANTES production in TEC, which may induce interstitial inflammation [30]. However, in vivo, HGF gene therapy has been shown to suppress macrophage infiltration after unilateral ureteral obstruction [31]. Blocking TGF-β1 diminishes TEC apoptosis and leads to increased proliferation of tubular epithelial cells after unilateral ureteral obstruction [32]. In contrast, endogenous, as well as exogenous, HGF

stimulates the proliferation of TEC [26, 33] and protects TEC from apoptosis after renal injury [31, 34–36].

Transforming growth factor-β1 has been shown to induce epithelial-mesenchymal transition in vitro [24], which can be blocked by HGF. Hence, HGF abrogates the α-SMA expression and E-cadherin suppression triggered by TGF-β1 in TEC. In addition, administration (even delayed) of recombinant HGF blocks myofibroblast accumulation in obstructive nephropathy [37, 38]. End-stage kidney disease is characterized by extensive interstitial fibrosis and glomerulosclerosis. The development of interstitial fibrosis can be prevented by TGF-β1 antisense oligodeoxynucleotides therapy in chronic obstructive nephropathy [39]. Administration of a blocking anti-HGF antibody increases renal fibrosis in rats with remnant kidneys [25]. Accordingly, the systemic administration of naked plasmid encoding HGF selectively prevents the accumulation and deposition of collagen type I and fibronectin in chronic obstructive nephropathy [24]. Hepatocyte growth factor exerts this in vivo anti-fibrogenic activity in part by counteracting TGF-β1 action through attenuation of one of its downstream mediators, connective tissue growth factor (CTGF) [40]. However, in an in vitro system, co-administration of TGF-β1 and HGF significantly increases the production of collagen type I, which is associated with an early enhanced CTGF induction [41]. Therefore, further investigations are necessary for definitive conclusions regarding this interaction. To what extent HGF is able to directly alter the synthesis of the ECM by TEC is still a matter of debate. In one study, HGF was shown to inhibit the expression and extracellular deposition of fibronectin by TEC [37], but Liu et al [25] indicated that HGF had no effect on ECM synthetic rate. Transforming growth factor-β1 inhibits MMP expression and induces expression of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), the endogenous inhibitors of MMP-9, thereby contributing to ECM accumulation. Hepatocyte growth factor markedly increases collagenase expression such as MMP-9 and decreases the expression of TIMP-1 and TIMP-2, resulting in matrix degradation [25].

In summary, TGF-β1 is a key modulator in renal fibrosis and HGF is a protective and anti-fibrotic factor during renal injury. Since both molecules share the same cellular source and are produced upon renal injury, the question arises which molecules may orchestrate their respective actions and may finally tip the balance, determining whether an injured kidney will repair or become fibrotic. One of the molecules that may modulate the balance between HGF and TGF-β1 is CD44.

The role of CD44 in progressive renal diseases

CD44 represents a family of cell surface–expressed glycoproteins encoded by one gene that consists of 19 exons. Through alternative RNA-splicing of up to 10 exons (v1 to v10), a large number of CD44 splice variants can be generated. CD44 is widely expressed and can be found on leukocytes, endothelial cells, and epithelial cells [42, 43]. The CD44 family is implicated in cell-cell and cell-matrix interaction, lymphocyte extravasation, tissue remodeling, and fibrosis and binding and presentation of growth factors [44, 45]. Hyaluronan and osteopontin are the two major ligands of CD44 [46]. CD44 isoforms expressing the domain encoded by exon v3 are decorated by heparan sulphate (CD44-HS) and therefore aquire unique functions. CD44-HS can act as a reservoir for cytokines and chemokines [47] and is able to bind growth factors and present these to their high-affinity receptors [48, 49]. In particular, CD44-HS binds HGF and presents it to its high affinity receptor, Met [50]. Besides facilitating the action of the reno-protective factor HGF, CD44 can also contribute to the pro-fibrotic actions of TGF-β1. CD44 provides a cell surface docking receptor for proteolytically active MMP-9, and MMP-9 localized at the cell surface is able to activate latent TGF-β1 [17]. Furthermore, upon binding with hyaluronan, CD44 interacts with TGF-β receptor I, leading to enhanced TGF-β1 signaling [51].

Under normal conditions, CD44 is undetectable in the kidney except in passenger leukocytes [52–54]. CD44 expression is markedly enhanced in inflammatory and chronic renal diseases, particularly on injured TECs in human nephropathies and in various animal models [44, 53, 55, 56]. We recently showed a strong correlation in immunoglobulin A (IgA) nephropathy between the tubulointerstitial expression of CD44 and the extent of glomerular and tubular damage and the degree of proteinuria [53]. The results of these studies suggest a key role for CD44 in the progression of renal diseases and prompted us to study the function of CD44 in chronic obstructive nephropathy using CD44 knock-out mice (CD44$^{-/-}$).

Early after obstruction, CD44$^{-/-}$ mice displayed significantly more tubular damage associated with less proliferation and more apoptosis of TECs compared to wild-type (WT) animals. Despite increased tubular damage, accumulation of myofibroblasts was less pronounced in CD44$^{-/-}$ than in WT mice and renal fibrosis was almost completely prevented in CD44$^{-/-}$ mice. In the first days following obstruction, renal homogenates of CD44$^{-/-}$ mice contained more HGF than those of WT mice. Despite this higher concentration of HGF in CD44$^{-/-}$ mice, the activation of c-Met, the high affinity receptor of HGF, was less compared to WT mice, suggesting an important role for CD44 in the signaling pathway of HGF in the kidney. The levels of TGF-β1 in renal homogenates of CD44$^{-/-}$ mice decreased in time, whereas TGF-β1 levels increased in WT mice. This was associated with an impaired signaling pathway of TGF-β1 in CD44$^{-/-}$ kidneys [57]. From this study, we concluded that CD44 is crucial

for the preservation of tubuli during renal injury, but promotes renal fibrosis through a cascade of events involving HGF and TGF-β1 signaling.

CONCLUSION

End-stage renal diseases are all characterized by extensive fibrosis that occurs via a common pathophysiologic pathway. Most patients with chronic renal diseases are identified before they reach terminal renal failure and would greatly benefit from therapeutic strategies that can stop or slow down the progression of renal fibrosis. Hepatocyte growth factor and TGF-β1, the two key molecules in this process, are excellent targets for therapy. Before starting clinical trials, more knowledge about the way both molecules are targeted to the damaged kidney, their interactions, their signaling pathways, and the role of other proteins, such as CD44, in this cascade of events are required.

REFERENCES

1. KLAHR S, MORRISSEY J: Obstructive nephropathy and renal fibrosis. *Am J Physiol Renal Physiol* 283:F861–875, 2002
2. EDDY AA: Molecular basis of renal fibrosis. *Pediatr Nephrol* 15:290–301, 2000
3. NANGAKU M, PIPPIN J, COUSER WG: C6 mediates chronic progression of tubulointerstitial damage in rats with remnant kidneys. *J Am Soc Nephrol* 13:928–936, 2002
4. VAN KOOTEN C, DAHA MR: Cytokine cross-talk between tubular epithelial cells and interstitial immunocompetent cells. *Curr Opin Nephrol Hypertens* 10:55–59, 2001
5. SHAPPELL SB, MENDOZA LH, GURPINAR T, et al: Expression of adhesion molecules in kidney with experimental chronic obstructive uropathy: The pathogenic role of ICAM-1 and VCAM-1. *Nephron* 85:156–166, 2000
6. NIKOLIC-PATERSON DJ, LAN HY, ATKINS RC: Macrophages in immune renal injury, in *Immunologic Renal Diseases*, 2nd edition, Philadelphia, Lippincott Williams & Wilkins, edited by NEILSON E, COUSER W, 2001, pp 609–632
7. NIKOLIC-PATERSON DJ, ATKINS RC: The role of macrophages in glomerulonephritis. *Nephrol Dial Transplant* 16:3–7, 2001
8. KANG DH, ANDERSON S, KIM YG, et al: Impaired angiogenesis in the aging kidney: Vascular endothelial growth factor and thrombospondin-1 in renal disease. *Am J Kidney Dis* 37:601–611, 2001
9. KANG DH, KANELLIS J, HUGO C, et al: Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol* 13:806–816, 2002
10. IWANO M, PLIETH D, DANOFF TM, et al: Evidence that fibroblasts derive from epithelium during tissue fibrosis. *J Clin Invest* 110:341–350, 2002
11. STRUTZ F, OKADA H, LO CW, et al: Identification and characterization of a fibroblast marker: FSP1. *J Cell Biol* 130:393–405, 1995
12. LENZ O, ELLIOT SJ, STETLER-STEVENSON WG: Matrix metalloproteinases in renal development and disease. *J Am Soc Nephrol* 11:574–581, 2000
13. STAHL PJ, FELSEN D: Transforming growth factor-beta, basement membrane, and epithelial-mesenchymal transdifferentiation: Implications for fibrosis in kidney disease. *Am J Pathol* 159:1187–1192, 2001
14. LIU Y: Hepatocyte growth factor and the kidney. *Curr Opin Nephrol Hypertens* 11:23–30, 2002
15. LIU Y, TOLBERT EM, SUN AM, DWORKIN LD: Primary structure of rat HGF receptor and induced expression in glomerular mesangial cells. *Am J Physiol* 271:F679–688, 1996
16. ABBATE M, ZOJA C, ROTTOLI D, et al: Proximal tubular cells promote fibrogenesis by TGF-beta1-mediated induction of peritubular myofibroblasts. *Kidney Int* 61:2066–2077, 2002
17. YU Q, STAMENKOVIC I: Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. *Genes Dev* 14:163–176, 2000
18. CRAWFORD SE, STELLMACH V, MURPHY-ULLRICH JE, et al: Thrombospondin-1 is a major activator of TGF-beta1 in vivo. *Cell* 93:1159–1170, 1998
19. CHU TM, KAWINSKI E: Plasmin, substilisin-like endoproteases, tissue plasminogen activator, and urokinase plasminogen activator are involved in activation of latent TGF-beta 1 in human seminal plasma. *Biochem Biophys Res Commun* 253:128–134, 1998
20. MATSUMOTO K, OKAZAKI H, NAKAMURA T: Up-regulation of hepatocyte growth factor gene expression by interleukin-1 in human skin fibroblasts. *Biochem Biophys Res Commun* 188:235–243, 1992
21. MATSUMOTO K, NAKAMURA T: Heparin functions as a hepatotrophic factor by inducing production of hepatocyte growth factor. *Biochem Biophys Res Commun* 227:455–461, 1996
22. WENG J, MOHAN RR, LI Q, WILSON SE: IL-1 upregulates keratinocyte growth factor and hepatocyte growth factor mRNA and protein production by cultured stromal fibroblast cells: Interleukin-1 beta expression in the cornea. *Cornea* 16:465–471, 1997
23. MIZUNO S, MATSUMOTO K, KUROSAWA T, et al: Reciprocal balance of hepatocyte growth factor and transforming growth factor-beta 1 in renal fibrosis in mice. *Kidney Int* 57:937–948, 2000
24. YANG J, DAI C, LIU Y: Systemic administration of naked plasmid encoding hepatocyte growth factor ameliorates chronic renal fibrosis in mice. *Gene Ther* 8:1470–1479, 2001
25. LIU Y, RAJUR K, TOLBERT E, DWORKIN LD: Endogenous hepatocyte growth factor ameliorates chronic renal injury by activating matrix degradation pathways. *Kidney Int* 58:2028–2043, 2000
26. KAWAIDA K, MATSUMOTO K, SHIMAZU H, NAKAMURA T: Hepatocyte growth factor prevents acute renal failure and accelerates renal regeneration in mice. *Proc Natl Acad Sci USA* 91:4357–4361, 1994
27. WRIGHT EJ, MCCAFFREY TA, ROBERTSON AP, et al: Chronic unilateral ureteral obstruction is associated with interstitial fibrosis and tubular expression of transforming growth factor-beta. *Lab Invest* 74:528–537, 1996
28. SCHIFFER M, VON GERSDORFF G, BITZER M, et al: Smad proteins and transforming growth factor-beta signaling. *Kidney Int Suppl* 77:S45–52, 2000
29. WAHL SM: TGF-beta in the evolution and resolution of inflammatory and immune processes. *Introduction. Microbes Infect* 1:1247–1249, 1999
30. WANG SN, LAPAGE J, HIRSCHBERG R: Role of glomerular ultrafiltration of growth factors in progressive interstitial fibrosis in diabetic nephropathy. *Kidney Int* 57:1002–1014, 2000
31. GAO X, MAE H, AYABE N, et al: Hepatocyte growth factor gene therapy retards the progression of chronic obstructive nephropathy. *Kidney Int* 62:1238–1248, 2002
32. MIYAJIMA A, CHEN J, LAWRENCE C, et al: Antibody to transforming growth factor-beta ameliorates tubular apoptosis in unilateral ureteral obstruction. *Kidney Int* 58:2301–2313, 2000
33. MILLER SB, MARTIN DR, KISSANE J, HAMMERMAN MR: Hepatocyte growth factor accelerates recovery from acute ischemic renal injury in rats. *Am J Physiol* 266:F129–134, 1994
34. VIJAYAN A, MARTIN DR, SADOW JL, et al: Hepatocyte growth factor inhibits apoptosis after ischemic renal injury in rats. *Am J Kidney Dis* 38:274–278, 2001
35. LIU Y: Hepatocyte growth factor promotes renal epithelial cell survival by dual mechanisms. *Am J Physiol* 277:F624–633, 1999

36. MIZUNO S, MATSUMOTO K, NAKAMURA T: Hepatocyte growth factor suppresses interstitial fibrosis in a mouse model of obstructive nephropathy. *Kidney Int* 59:1304–1314, 2001
37. YANG J, DAI C, LIU Y: Hepatocyte growth factor gene therapy and angiotensin II blockade synergistically attenuate renal interstitial fibrosis in mice. *J Am Soc Nephrol* 13:2464–2477, 2002
38. YANG J, LIU Y: Delayed administration of hepatocyte growth factor reduces renal fibrosis in obstructive nephropathy. *Am J Physiol Renal Physiol* 284:F349–357, 2003
39. ISAKA Y, TSUJIE M, ANDO Y, et al: Transforming growth factor-beta 1 antisense oligodeoxynucleotides block interstitial fibrosis in unilateral ureteral obstruction. *Kidney Int* 58:1885–1892, 2000
40. INOUE T, OKADA H, KOBAYASHI T, et al: Hepatocyte growth factor counteracts transforming growth factor-beta1, through attenuation of connective tissue growth factor induction, and prevents renal fibrogenesis in 5/6 nephrectomized mice. *FASEB J* 17:268–270, 2003
41. INOUE T, OKADA H, KOBAYASHI T, et al: TGF-beta1 and HGF coordinately facilitate collagen turnover in subepithelial mesenchyme. *Biochem Biophys Res Commun* 297:255–260, 2002
42. BENZ PS, FAN X, WUTHRICH RP: Enhanced tubular epithelial CD44 expression in MRL-lpr lupus nephritis. *Kidney Int* 50:156–163, 1996
43. GRIFFIOEN AW, COENEN MJ, DAMEN CA, et al: CD44 is involved in tumor angiogenesis; an activation antigen on human endothelial cells. *Blood* 90:1150–1159, 1997
44. GUNTHERT U: CD44: A multitude of isoforms with diverse functions. *Curr Top Microbiol Immunol* 184:47–63, 1993
45. LESLEY J, HYMAN R, KINCADE PW: CD44 and its interaction with extracellular matrix. *Adv Immunol* 54:271–335, 1993
46. SIEGELMAN MH, DEGRENDELE HC, ESTESS P: Activation and interaction of CD44 and hyaluronan in immunological systems. *J Leukoc Biol* 66:315–321, 1999
47. TANAKA Y, ADAMS DH, HUBSCHER S, et al: T-cell adhesion induced by proteoglycan-immobilized cytokine MIP-1 beta. *Nature* 361:79–82, 1993
48. JACKSON DG, BELL JI, DICKINSON R, et al: Proteoglycan forms of the lymphocyte homing receptor CD44 are alternatively spliced variants containing the v3 exon. *J Cell Biol* 128:673–685, 1995
49. VAN DER VOORT R, KEEHNEN RM, BEULING EA, et al: Regulation of cytokine signaling by B cell antigen receptor and CD40-controlled expression of heparan sulfate proteoglycans. *J Exp Med* 192:1115–1124, 2000
50. VAN DER VOORT R, TAHER TE, WIELENGA VJ, et al: Heparan sulfate-modified CD44 promotes hepatocyte growth factor/scatter factor-induced signal transduction through the receptor tyrosine kinase c-Met. *J Biol Chem* 274:6499–6506, 1999
51. BOURGUIGNON LY, SINGLETON PA, ZHU H, ZHOU B: Hyaluronan promotes signaling interaction between CD44 and the TGF-β RI in metastatic breast tumor cells. *J Biol Chem* 277:39703–39712, 2002
52. TAKAZOE K, FOTI R, TESCH GH, et al: Up-regulation of the tumour-associated marker CD44V6 in experimental kidney disease. *Clin Exp Immunol* 121:523–532, 2000
53. FLORQUIN S, NUNZIATA R, CLAESSEN N, et al: CD44 expression in IgA nephropathy. *Am J Kidney Dis* 39:407–414, 2002
54. SCREATON GR, BELL MV, JACKSON DG, et al: Genomic structure of DNA encoding the lymphocyte homing receptor CD44 reveals at least 12 alternatively spliced exons. *Proc Natl Acad Sci USA* 89:12160–12164, 1992
55. DOUGHERTY GJ, LANDORP PM, COOPER DL, HUMPHRIES RK: Molecular cloning of CD44R1 and CD44R2, two novel isoforms of the human CD44 lymphocyte "homing" receptor expressed by hemopoietic cells. *J Exp Med* 174:1–5, 1991
56. TOLG C, HOFMANN M, HERRLICH P, PONTA H: Splicing choice from ten variant exons establishes CD44 variability. *Nucleic Acids Res* 21:1225–1229, 1993
57. ROUSCHOP KMA, SEWNATH ME, CLAESSEN N, et al: CD44 protects kidneys in vivo from tubular damage but promotes fibrosis through alteration of HGF/cMet and TGF-β1 signaling pathways. *J Am Soc Nephrol* 13:162A, 2002