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Review

Hepatocyte growth factor in renal disease: cause or cure?

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Abstract. Hepatocyte growth factor (HGF) is an injury-released growth factor with diverse effects on epithelial and endothelial cells. These effects include proliferation, migration, extracellular matrix production and tubulogenesis. These activities allow HGF to function as an organizer of repair processes that bring about restoration of tubular function following renal injury. However, while HGF has been demonstrated to accelerate recovery of renal function after an acute insult, prolonged exposure to elevated levels of HGF can reduce renal function and may contribute to progressive renal disease. This review will describe the cellular activities of HGF, how they pertain to renal repair and the therapeutic application of regulating HGF activity in acute versus chronic renal disease.

Key words. Hepatocyte growth factor; c-met; renal disease; diabetes; glomerulosclerosis.

Introduction

Hepatocyte growth factor (HGF) is a large plasminogen-related growth factor with multiple cellular effects that are important to development and tissue regeneration. Although it was first described as a growth factor for hepatocytes [1], HGF has been shown to be an important factor in renal organogenesis and in renal injury. HGF stimulates the growth of renal epithelial cells (mitogen), enhances the motility of epithelial cells (motogen) and induces renal epithelial tubule formation (morphogen) [2–4] by acting on the single trans-membrane tyrosine kinase receptor c-met. The HGF axis is activated following injury and is likely to be a critical factor in renal remodeling. For example, HGF expression and its receptor c-met are increased in the kidney following nephrectomy or ischemia [5], and acute administration of HGF improves renal function following $HgCl_2$ administration or ischemia [6, 7]. There is also evidence that expression of the HGF receptor, c-met, is elevated in the kidneys of rats with streptozotocin-induced diabetes [8]. Although serum HGF levels are elevated in patients with progressive renal disease [9], the effect of chronically elevated HGF levels on renal function in humans is unknown. This review will examine the evidence for the role of HGF in renal failure and address the effects of HGF in acute versus chronic disease.

Cellular effects of HGF

HGF is a pleiotropic factor that significantly affects organogenesis and organ regeneration. One of the most immediate effects of HGF on renal epithelial cells is the induction of scattering, hence it is also known as scatter factor [4, 10–12]. HGF can induce scattering and cell motility in a variety of epithelial and endothelial cells. For example, keratinocytes [13], endometrial epithelial cells [14], myoblasts [15, 16], pancreatic oval cells [17], chondrocytes [18], corneal epithelial cells [19], vascular endothelial cells [20] and brain endothelial cells [21] migrate in response to HGF in vitro. Initial observations described that HGF specifically induced scattering

or migration of epithelial cells but not fibroblasts or epithelial cells from tumor cell lines [12, 22]. However, more recent evidence suggests that several epithelial cancer cell lines from renal carcinoma [23], colorectal adenocarcinoma [24] and ovarian carcinoma [25] also scatter in response to HGF. Thus, cells with epithelial characteristics, regardless of tissue source, respond uniquely to HGF with scattering and migration.

HGF is also a potent stimulator of epithelial cell proliferation. HGF increases proliferation of renal epithelial cells [26], intestinal epithelial cells [27], tracheal epithelial cells [28] and hepatocytes [29]. The proliferative effect of HGF also overrides the growth arrest induced by transforming growth factor-β in renal epithelial, lung epithelial and vascular endothelial cells [30]. Most studies suggest that, within the kidney, HGF primarily increases proliferation of renal epithelial cells but not glomerular mesangial cells [31, 32]. However, recent evidence has shown that glomerular mesangial cells proliferate in response to HGF, albeit with a modest 1.6-fold increase [33]. While mesangial cells clearly have functional HGF receptors [32–34], the function of HGF on mesangial cells still remains to be determined and is clearly different than its role with respect to epithelial cells.

HGF can also increase the production of extracellular matrix by renal cells. Mesangial cells and renal epithelial cells increase synthesis of extracellular matrix in response to HGF, including fibronectin and collagen α1-IV [35]. Autocrine expression of HGF-transfected mIMCD-3 cells resulted in increased expression of fibronectin messenger RNA (mRNA) [36]. In addition, opossum kidney cells have increased fibronectin expression following HGF transfection [36]. Another matrix marker, plasminogen activator inhibitor, was also elevated in response to HGF in HepG2 epithelial hepatoblastoma cells [37]. While the ability of mesangial cells to produce fibronectin in response to HGF may depend on the environmental milieu [34], clearly HGF promotes extracellular matrix deposition in cells of epithelial origin.

One of the most visually dramatic effects of HGF on epithelial cells is the induction of tubules. Madin Darby canine kidney (MDCK) cells can form tubules with a distinct lumen in response to HGF when grown in type 1 collagen [2]. This activity is in part responsible for the phenomenon of renal mesenchyme-induced tubulogenesis in the developing kidney. In support of this hypothesis, neutralizing antibodies against HGF can prevent isolated mesenchyme from inducing tubule formation of MDCK cells in vitro [38]. The tubulogenic effect of HGF is not limited to MDCK cells but was also observed in epithelial cells derived from the ureteric bud [39], murine inner medullary collecting duct epithelial cells [4], as well as epithelial cells from other tissues such as the mammary gland epithelial cells [40]. This evidence clearly implicates HGF in growth and development of renal tubular structures. However, it is also evident that HGF is not the sole factor responsible for tubulogenesis. Knockout mice that lack the functional HGF receptor c-met or lack HGF had seemingly normal renal development up to gestational day 14, after which placental and liver defects prevented further development [41–43]. Moreover, epidermal growth factor (EGF) and transforming growth factor-α also induced tubulogenesis in murine inner medullary collecting duct cells (mIMCD3) [39, 44]. Nevertheless, HGF supports tubulogenesis and appears to be involved in establishing the mature renal cytoarchitecture of the functioning kidney.

HGF signaling pathways

HGF causes these pleiotropic effects by activating the single transmembrane tyrosine kinase receptor c-met. Met was originally isolated as an oncogene from a human osteogenic sarcoma cell line [45, 46]. Based on sequence homology, the full-length c-met protooncogene has characteristics common to tyrosine kinase growth factor receptors [47] and was identified as the receptor for HGF [48, 49]. Similar to other tyrosine kinase receptors, c-met consists of an extracellular α chain that is disulfide-linked to a single transmembrane β chain. That c-met is responsible for the pleiotropic activity of HGF was demonstrated with the expression of a hybrid receptor made of the binding domain of nerve growth factor (NGF) and the cytoplasmic domain of c-met in MDCK cells [50]. MDCK cells expressing the chimeric receptor display all the mito-, moto- and morphogenic responses following NGF treatment that are normally associated with HGF [50]. The HGF receptor is expressed in epithelial cells of most tissues with highest expression in the adult mouse kidney [51] and suggests that HGF is not only important during development but may also have roles in maintaining epithelial functions which are particularly prominent in the kidney.

Subsequent to ligand binding the intracellular domain of the c-met β chain autophosphorylates, which is a requirement for activity [48–54]. Several substrates and docking proteins that associate with the kinase domain of c-met have been identified and are linked to the various activities of HGF. Proteins that are activated by c-met include phosphoinositide 3-kinase (PI-3-kinase), phospholipase Cγ, pp60^{src}, Grb2-SoS complex and STAT-3. HGF-induced scattering and tubule formation of inner medullary collecting duct cells was inhibited by the PI-3-kinase inhibitor Wortmannin [55], suggesting that PI-3 kinase mediates these effects. In addition,

phosphorylation of the transcription factor STAT-3 by c-met is involved in mediating HGF-induced branching morphogenesis [56]. Finally, mutations in c-met that prevent the association of Grb2 with c-met prevent HGF-induced proliferation [57], and $pp60^{src}$ mediates effects on proliferation [26, 58] (fig. 1). Thus, the HGF receptor c-met activates several second-messenger pathways that are selectively responsible for mediating the various pleiotropic activities of HGF.

Expression of HGF and c-met in renal failure

It is evident from the potent and diverse processes that are induced by HGF in renal tissue that HGF plays an important role in kidney development and most likely has significant effects on the progression of renal disease and the repair of renal injury. Increased expression of either HGF or c-met can be demonstrated in several acute renal disease models. HGF and c-met expression are increased in the kidney following folic acid-induced renal failure [59] and with $HgCl_2$-induced renal damage [60]. These models resemble data obtained from patients with acute renal failure where serum and urine levels of HGF were dramatically increased compared to patients with no renal disease or with cystic renal disease [61, 62].

Renal ischemia increased the mRNA levels for c-met specifically in the kidney and not in other organs [5]. However, HGF mRNA was elevated not only in the kidney but also nonspecifically in the liver [5] and may account for the systemic increase in HGF protein found in serum of acute renal failure patients [62]. Thus, upregulation of the renal HGF receptor offers some specificity for HGF activity. A further level of selectivity is achieved with a serine protease, HGF activator, that proteolytically activates the single-chain HGF only in the injured organ [63–65]. HGF activity can therefore be confined to the injured tissue by selective expression of c-met and the HGF activator.

Increased expression of HGF or c-met can also be demonstrated in animal models of chronic renal disease. Induction of compensatory renal hypertrophy by uninephrectomy is associated with increased levels of HGF and c-met [5]. Further evidence that HGF plays a role in chronic renal disease is that c-met is elevated in the kidneys of rats with streptozotocin-induced diabetes [8]. Glucose levels appear to mediate this effect on the kidney because the increased expression of c-met was partially reversed by insulin treatment. Moreover, high glucose levels increased c-met expression in cultured renal cells [8]. Therefore, HGF and c-met activation is increased in progressive renal disease as well as following acute renal injury.

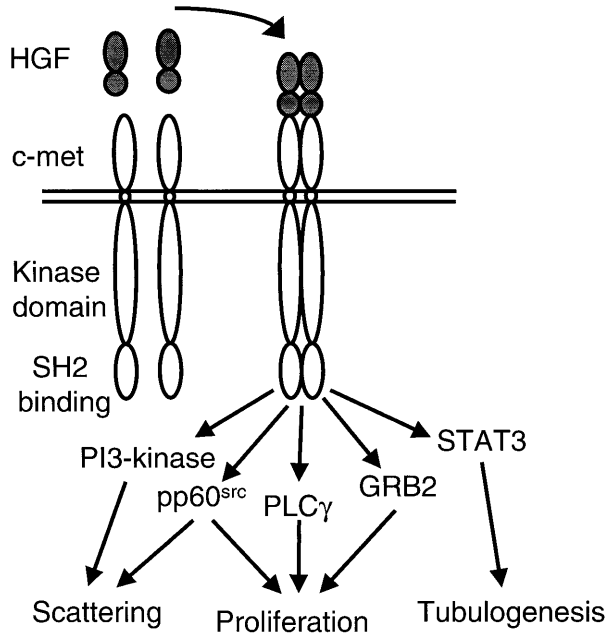

Figure 1. Model of second messengers involved in HGF-induced cell scattering, proliferation and tubulogenesis. The N-terminal domain of HGF primarily interacts with the ligand binding domain of c-met. Upon the requisite dimerization of c-met and receptor autophosphorylation, the SH2 domains of PI3-kinase, $pp60^{src}$, PLC-γ, GRB2, and STAT3 bind the c-met receptor, which leads to activation of these proteins and subsequent changes in cellular behavior.

Therapeutic indications

The potent effects of HGF on cells in vitro, the evidence of c-met expression in the above models and HGF measurements in human patients suggest that modulating the levels of HGF activity would effect the progression of renal disease (table 1). The strongest evidence for a beneficial role of HGF in renal disease is demonstrated in models of acute renal failure. Recombinant human HGF given 30 min post-reperfusion subcutaneously reduced serum creatinine levels and improved renal histology in rats with transient renal ischemia [7]. In support of this study, $HgCl_2$-induced renal injury in mice was also reduced by daily injections of HGF into the tail vein [6]. Six injections of recombinant human HGF (100 μg/kg) prevented the fourfold increase in blood urea nitrogen concentrations and gross histological changes, including tubular hyperplasia. These studies suggest that elevations in HGF and the receptor c-met are part of a compensatory mechanism following acute injury, which assists in the repair process and restoration of renal function. Indeed, HGF reduced apoptosis in renal epithelial cells, revealing another

Table 1. Effects of HGF in renal disease.

Disease/model	Species	Effect of HGF	Ref.
Acute			
Ischemia	rat	improved renal function	[7]
HgCl2	mouse	improved renal function improved histology	[6]
Chronic			
ICGN	mouse	reduced albuminuria reduced glomerulosclerosis	[68]
HGF transgenic	mouse	renal interstitial fibrosis glomerulosclerosis polycystic kidney	[69]
HGF/NK1 transgenic	mouse	moderate glomerulosclerosis and tubular hyperplasia	[70]
HGF infusion	*db* mouse	increased proteinuria reduced creatinine clearance	[35]

mechanism besides stimulation of proliferation by which HGF can ameliorate renal injury [66, 67].

The benefits of prolonged HGF exposure in chronic renal failure appear to be less clear. Daily injections of HGF (500 μg/kg) for 28 days prevented the loss of renal function in the nephrotic mouse strain ICGN [68]. The ICGN mice develop proteinuria and glomerulosclerosis naturally, and HGF treatment prevented the progression of the disease, including the deposition of extracellular matrix components such as fibronectin and collagen as well as growth factors that stimulate matrix deposition such as transforming growth factor β and platelet-derived growth factor [68]. Whether HGF could also reverse glomerulosclerosis and tubular hyperplasia once it has already developed in this model remains to be determined.

In contrast, two different transgenic mouse models showed that overexpressing HGF, or the partial HGF agonist HGF/NK1, in a normal mouse background caused mice to develop progressive renal disease [69, 70]. Mice overexpressing HGF in the kidney and serum developed severe renal disease with characteristic changes in glomerular and tubular morphology. Glomeruli, which were normal at birth, changed with age and developed focal segmental glomerulosclerosis with increased mesangial matrix and thickening of the basement membranes. Moreover, continuous exposure to high levels of HGF also caused changes in tubular morphology consistent with tubular hyperplasia and interstitial fibrosis. Overexpression of the partial agonist HGF/NK1, which is a naturally occurring alternatively spliced N-terminal truncated form of HGF that includes the first kringle domain [71], also induces progressive renal disease [70]. However, the severity of the disease was milder, which is consistent with its weaker agonist activity [71]. As with the HGF transgenic mouse, neonatal HGF/NK1 transgenics had normal renal morphology that progressed to glomerulosclerosis and tubular hyperplasia as the mice got older. This brings into serious question whether HGF should be used as a therapeutic for chronic renal disease.

Another mouse strain that develops progressive renal disease is the leptin receptor mutant diabetic mouse (*db*/*db*). These mice are obese and mildly diabetic and show increased microalbuminuria and decreased creatinine clearance with age [72, 73]. When these mice are treated with HGF by a continuous 21-day infusion using an intraperitoneally placed osmotic infusion pump, the loss of renal function is accelerated as determined by microalbuminuria and creatinine clearance (fig. 2; [35]). This is in contrast to the effects of HGF in the ICGN mouse. Whether the strain differences or dosing modalities account for the different results awaits studies done in other models of chronic renal

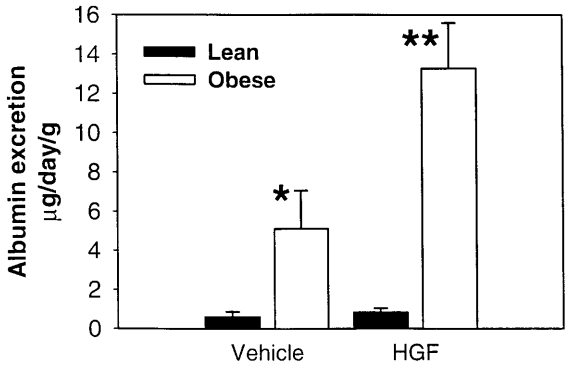

Figure 2. HGF was given to lean and obese *db* mice for 18 days by Alzet miniosmotic pump s.c. at an estimated rate of 160 ng/day. Obese mice had a 10-fold increase in urine flow, a nearly 2-fold increase in serum creatinine levels and 5-fold higher albumin excretion than lean mice. Chronic HGF administration further reduced renal function in obese mice as seen with significantly increased albumin excretion [35].

disease. However, the effects of HGF in the *db*/*db* mouse support the findings seen in transgenic mice that prolonged exposure to HGF leads to loss of renal function.

Conclusions and perspective

HGF is a pleiotropic factor that has profound effects on renal epithelial cell activity, morphology and organization. These functions suggest that HGF is a critical renotrophic factor involved in renal repair, which is supported by two lines of evidence. First, HGF and its receptor c-met are rapidly increased in the kidney following renal injury. Second, administration of HGF accelerates recovery of renal function and maintenance of normal renal morphology after an acute insult. However, continuous exposure to high levels of HGF may contribute to progressive renal disease. Thus, by borrowing from the future to repair the present, HGF restores renal function rapidly after an insult but can contribute to renal disease if the insults are repeated or chronic as in diabetic nephropathy. The very mechanisms that HGF uses to repair the injured tubules, such as proliferation and matrix deposition, can cause morphological changes in glomeruli that presumably impair filtration functions and over time may lead to glomerulosclerosis. While HGF is clearly beneficial in acute rodent models of renal disease, the potential benefit of inhibiting HGF in chronic renal disease can only be substantiated once inhibitors of HGF are applied to these respective conditions.

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