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BRIEF REPORT

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Serum HGF levels in acute renal rejection after living related renal transplantation

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Abstract Hepatocyte growth factor (HGF), a long sought-after hepatotrophic factor, has recently been shown to act as a renotrophic factor in regeneration of the kidney. We investigated serum HGF levels in 16 renal transplant patients. In patients with acute rejection, the serum HGF level was markedly increased (over 1 ng/ml), and its elevation was accompanied by an increase in serum creatinine and blood urea nitrogen (BUN). In contrast, serum HGF levels were continuously low in patients without rejection. We conclude that serum HGF may become a clinically useful marker for the assessment of acute renal rejection.

Key words Kidney transplantation, hepatocyte growth factor · Rejection, kidney transplantation, hepatocyte growth factor · Hepatocyte growth factor, rejection, kidney transplantation

Introduction

Hepatocyte growth factor (HGF) was first identified in serum from partially hepatectomized rats as a potent mitogen for mature hepatocytes [3]. HGF is a heterodimetric molecule composed of a 69-kDa kringle-containing α-chain and a 34-kDa β-chain [5], and it elicits mitogenic, motogenic, and morphogenic responses from various types of cells [3]. Although HGF has been well characterized as a hepatotrophic factor in liver regeneration [3], this growth factor has also recently been shown to act as a renotrophic factor in renal regeneration [2, 4]. The expression of HGF is rapidly and markedly induced following experimentally induced acute renal failure and unilateral nephrectomy. More importantly, intravenous injection of recombinant HGF into mice or rats strongly suppresses the onset of severe renal dysfunction and stimulates renal regeneration after acute renal failure caused by cisplatin, $HgCl_2$, and ischemia [2, 4]. These results indicate that HGF may well have potential as a novel drug for preventing the damage of acute renal failure and for enhancing renal regeneration.

Because of this potent renotrophic function of HGF and its diagnostic and therapeutic potential for renal dysfunction, we measured serum HGF levels in patients after renal transplantation. We found that the serum HGF level increases at acute renal rejection and that detection of rejection is possible based on HGF levels.

Materials and methods

Patients

Serum HGF levels were measured in 16 patients who underwent living related renal transplantation at our institutions between November 1992 and May 1995. There were 14 men and 2 women, aged 14–44 years (mean age 31 years). Acute renal rejection occurred 13 times in ten patients, while no rejection occurred in six patients. The diagnosis of acute rejection was based on histological

Table 1 Serum HGF and creatinine levels during acute renal rejection and after renal transplantation

Patient number	Age	Sex	Maximum creatinine (mg/dl)	Maximum HGF (ng/ml)
R1.1[a]	32	Male	4.7	4.75
R1.2			1.8	2.36
R2	25	Male	3.4	3.51
R3.1	34	Male	3.4	3.55
R3.2			6.2	1.23
R4	23	Male	7.4	2.26
R5	14	Male	11.8	2.33
R6	39	Male	5.7	1.68
R7.1	22	Male	2.4	1.54
R7.2			1.8	1.79
R8	35	Male	5.5	1.10
R9	19	Male	6.6	1.06
R10	41	Male	3.6	1.08
Mean			4.9	2.17*
S1[b]	21	Female	1.2	0.53
S2	25	Male	1.3	0.97
S3	42	Male	1.8	0.27
S4	37	Male	1.8	0.86
S5	44	Male	1.7	0.57
S6	42	Female	0.8	0.58
Mean			1.4	0.63*

* $P < 0.01$

[a] R1–R10: patients with acute renal rejection

[b] S1–S6: patients without rejection

examination of biopsies of the renal allografts. Treatment was mainly based on immunosuppressive therapy that included methylprednisolone, antilymphocyte immunoglobulin, muromonab CD3 (OKT 3) and 15-deoxyspergualin.

Assay

Serum HGF levels were determined by an enzyme-linked immunosorbent assay using an HGF test kit (Institute of Immunology, Tokyo, Japan). The serum HGF level in healthy individuals is less than 0.29 ng/ml. None of the patients had any obvious clinical signs of hepatic dysfunction, which is known to be associated with an increase in the serum levels of this factor. The Mann-Whitney U-test was used to compare the mean serum HGF levels and the percent increase in the serum HGF among the different subgroups of patients.

Results

Figure 1 shows the typical pattern of the changes in serum creatinine, blood urea nitrogen, and serum HGF in three patients (two patients with acute rejection and one patient without rejection). In one of the patients who experienced acute rejection, the serum HGF level increased just after surgery and then decreased to baseline by 10 days postoperatively (Fig. 1 a). However, it increased rapidly when acute renal rejection occurred. Serum HGF levels then decreased soon after treatment was started, along with recovery of renal function, suggesting that the HGF was produced in the early phase of renal rejection. Similar results were obtained in another patient who suffered acute rejection (Fig. 1 b). It seems that the serum HGF level increased just before the onset of severe acute renal rejection. In contrast, in the patient without rejection, the serum HGF never rose beyond 1 ng/ml (Fig. 1 c). A substantially similar relationship between HGF levels and acute rejection was found in another seven patients.

Figure 2 shows the serum HGF levels of normal volunteers and the maximum serum HGF levels in our patients. In the latter, the serum HGF level increased during acute renal rejection to over 1 ng/ml (mean 2.17 ± 1.14 vs 0.29 ± 0.09 ng/ml in normal controls; $P < 0.01$). Moreover, the maximum serum HGF level during acute renal rejection was significantly higher than the maximum serum HGF level in the patients without rejection after transplantation (mean 2.17 ± 1.14 vs 0.63 ± 0.25; $P < 0.01$). Overall, abnormal data were found in all patients with acute renal rejection and, in some cases, the serum HGF level rose earlier than the serum creatinine. The serum HGF level in acute renal rejection was correlated with both clinical features at presentation and the subsequent course. Increased serum levels (over 1 ng/ml) of HGF were detected in all of the steroid-resistant acute renal rejections.

Discussion

HGF was first identified as a hepatotrophic factor, so serum HGF levels were mainly measured in patients with liver dysfunction [7, 8]. Recent reports reveal that HGF is one of the strongest mitogens of renal tubular cells [1] and that the paracrine system causes it to be immediately excreted from kidney interstitial cells when there is acute renal tubular damage [2]. Whereas steroid-resistant acute renal rejection causes severe renal tubular damage and leads to renal tubular cell regeneration, HGF may trigger the recovery from renal tubular damage.

Many cellular interactions in acute rejection are mediated by cytokines, but while many parameters, such as IL-6 [9] or IL-2 receptor [6] levels, have been reported to be markers of rejection, no useful marker has previously been known to evaluate the acute renal rejection. We obtained evidence that the serum HGF level increases at the onset of acute renal rejection but that it does not increase in patients without rejection. The reason why HGF increases at the onset of acute rejection has yet to be investigated, but we speculate that induction of HGF may occur in the kidney and other organs in response to cellular damage in the renal tubular cells

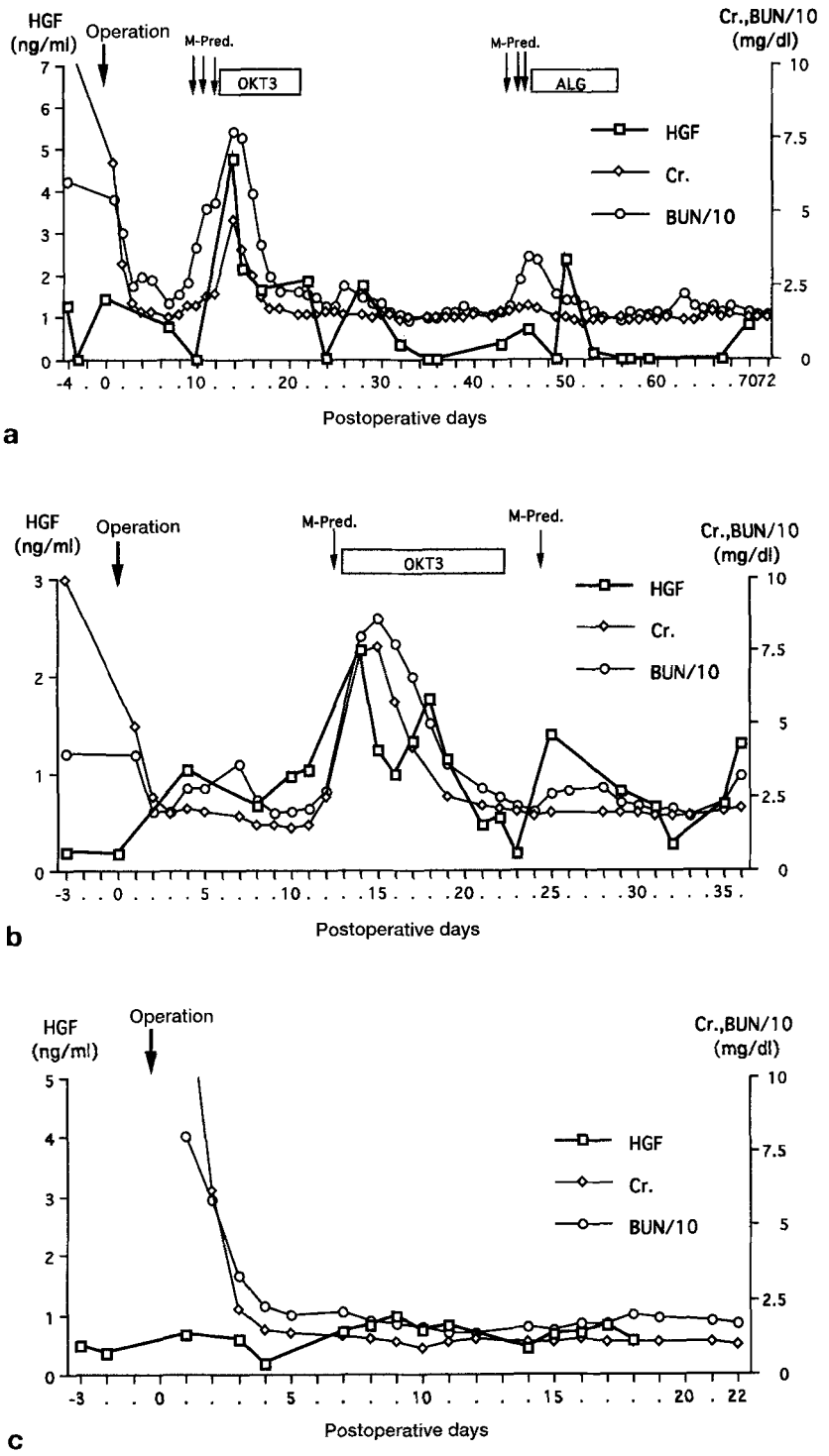
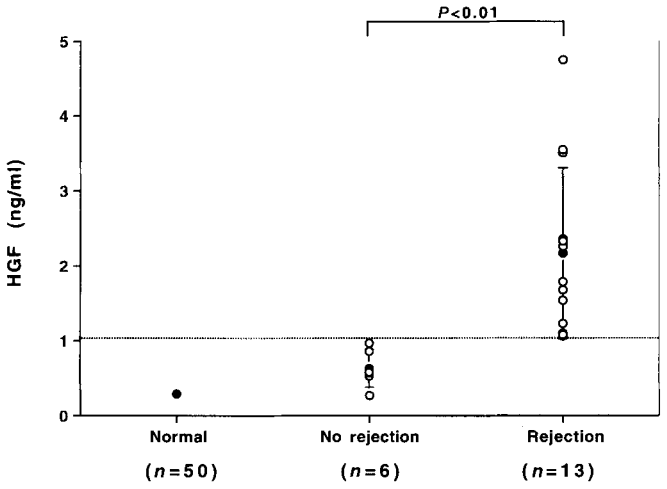


Fig. 1 a–c Clinical course and serum HGF and creatinine levels in living related renal transplant recipients: **a** patient 1 with rejection; **b** patient 2 with rejection; **c** patient 3 without rejection

rather than as part of a systemic immunological response. In rat experiments HGF originated from kidney interstitial cells using in situ hybridization [2]. Moreover, we found that the HGF level during the early phase of rejection.

Taken together with the finding that injection of recombinant HGF accelerates renal regeneration in mice and rats [2, 4], our finding that high levels of HGF are associated with acute renal rejection suggests that this factor could be used to accelerate renal regeneration



and the restoration of renal function after a rejection episode in humans as well. In sum, the serum HGF level in renal transplant patients may be useful for the evaluation of acute renal rejection.

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Fig. 2 Serum HGF levels of normal controls and maximum serum HGF level of patients after renal transplantation (○ serum creatinine values of the patients; ● mean values of serum creatinine and standard deviations)

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