Available online at www.sciencedirect.com
SCIENCE DIRECT®
Biochemical and Biophysical Research Communications 324 (2004) 341–347
BBRC
www.elsevier.com/locate/ybbrc

Effect of hematopoietic cytokines on renal function in cisplatin-induced ARF in mice

Masashi Nishida*, Shin-ichiro Fujimoto, Kentaro Toiyama, Hisashi Sato, Kenji Hamaoka

Department of Pediatric Cardiology and Nephrology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan

Received 30 August 2004
Available online 25 September 2004

Abstract

In this study, the effect of hematopoietic cytokines, i.e., granulocyte-colony stimulating factor (G-CSF), stem cell factor (SCF), and granulocyte–macrophage-colony stimulating factor (GM-CSF), on renal function was studied in cisplatin-induced acute renal failure in mice. Treatment with G-CSF significantly ameliorated both BUN and serum creatinine increase induced by cisplatin administration with concomitant alleviation in the degree of necrotic change, enhancement in DNA synthesis, and decrease in apoptosis of renal tubular cells. There was no significant change observed among these parameters following treatment with SCF or with GM-CSF. Serum hepatocyte growth factor level was significantly lower in mice treated with cisplatin and G-CSF compared with that in those treated with cisplatin only. In conclusion, G-CSF, but not SCF or GM-CSF, acts to accelerate regeneration and prevent apoptosis of renal tubular epithelial cells and leads to reduced renal injury in cisplatin-induced acute renal failure in mice.

Keywords: Hematopoietic cytokines; Granulocyte-colony stimulating factor; Stem cell factor; Granulocyte–macrophage-colony stimulating factor; Acute renal failure; Acute tubular necrosis; Renal tubular regeneration; Cisplatin

Nephrotoxic and ischemic insults to the kidney lead to acute renal failure (ARF) and most often manifest as acute tubular necrosis. Recovery of renal function following ARF is dependent on the replacement of necrotic tubular cells with functional tubular epithelium. The source of these new tubular cells has been thought to be resident renal tubular cells [1]. However, recent studies have demonstrated that bone marrow stem cells from both mice and humans have the ability to cross lineage boundaries and form functional components of other tissues such as heart, liver, brain, skeletal muscle, and vascular endothelium [2,3]. The contribution of bone marrow cells to regeneration following renal damage has also been indicated [4–7], and it has been reported more recently that hematopoietic bone marrow stem cells that are mobilized into the circulation appear to participate in the regeneration of the necrotic tubules to a great extent following ischemically induced acute tubular necrosis in mice [8,9]. These observations, as a matter of course, evoked potential therapeutic strategies aimed at enhancing the mobilization of bone marrow stem cells to the kidney as entirely new approaches for the treatment of acute tubular necrosis.

cis-Diamminedichloroplatinum (cisplatin) is a widely used antitumor drug, however the major problem with its use is a high incidence of nephrotoxicity and renal dysfunction, mainly in the form of renal tubular damage, leading to impaired glomerular filtration [10]. In this study, we thus intended to examine the effects of several cytokines that stimulate the mobilization of bone marrow stem cells to peripheral circulation, i.e., granulocyte-colony stimulating factor (G-CSF), stem cell factor (SCF), and granulocyte–macrophage-colony

* Corresponding author. Fax: +81 75 251 5833.
E-mail address: mnishida@koto.kpu-m.ac.jp (M. Nishida).

0006-291X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2004.09.051

stimulating factor (GM-CSF) on renal function in a mouse model of cisplatin-induced ARF, to test the potential clinical usefulness of these agents for the treatment of acute tubular necrosis.

Methods

Animal treatments. Experiments were performed on male C57BL/6 mice (10–12 weeks, 20–24 g). Acute renal injury was induced by subcutaneous administration of cisplatin (15 mg/kg; Nippon Kayaku, Tokyo, Japan) in 0.5 ml saline. For the cytokine treatment, mice were injected s.c. with either recombinant human G-CSF, 50 μg/kg (Chugai Pharmaceutical, Tokyo, Japan), recombinant mouse SCF, 200 μg/kg (Kirin Brewery, Tokyo, Japan), recombinant mouse GM-CSF, 80 μg/kg (Kirin Brewery) in 0.5 ml of saline, or saline alone at the time of cisplatin administration and 6, 24, 48, and 72 h after cisplatin administration. Mice were sacrificed 96 h after cisplatin administration, then the kidneys were harvested and subjected to the studies described below. The experimental protocols were performed according to the regulations of the Kyoto Prefectural University of Medicine Animal Care Committee.

Hematologic analysis and measurement of blood urea nitrogen, serum creatinine, and hepatocyte growth factor. At sacrifice, blood samples were collected by retro-orbital venous plexus puncture for determination of leukocyte count and blood urea nitrogen (BUN), serum creatinine, and hepatocyte growth factor (HGF) concentrations. Blood samples for determination of BUN and serum creatinine were also collected at 24 and 48 h after cisplatin administration. BUN was measured by the urease-ultraviolet method, and serum creatinine was measured by enzymatic method using a H-7170S autoanalyzer (Hitachi, Tokyo, Japan). HGF was measured by enzyme-linked immunosorbent assay following the manufacturer's protocol (Otsuka Pharmaceutical, Tokyo, Japan). Total and differential leukocyte count was determined using a SE9000 automated counter (Sysmex, Kobe, Japan).

Histological study. For histological examinations, kidneys were fixed with 4% buffered paraformaldehyde for 6 h, embedded in paraffin, and sectioned transversely with a thickness of 4 μm. The sections were stained with periodic acid–Schiff (PAS) and by immunohistochemistry to detect CD45-positive cells, proliferating cells, and apoptotic cells. Frozen sections of the kidney were also used for immunohistochemical staining of CD34 and c-kit.

To detect CD45-positive cells, after antigen retrieval and quenching with 3% hydrogen peroxide in methanol, sections were incubated with monoclonal rat anti-mouse CD45 (Leukocyte Common Antigen, Ly-5; 1:10 dilution; BD Biosciences, San Jose, CA, USA) followed by standard ABC immunostaining. To detect CD34-positive cells and c-kit-positive cells, 8-μm-thick frozen sections were incubated with monoclonal rat anti-mouse CD34 (1:10 dilution; BD Biosciences) and polyclonal rabbit anti-human c-kit (CD117; 1:50 dilution; DAKO, Carpinteria, CA, USA), respectively, followed by standard ABC immunostaining using ABC-alkaline phosphatase kit (Vector, Burlingame, CA, USA). The efficacy of these antibodies to detect hematopoietic cells was confirmed in the sections of mouse spleen tissue.

The bromodeoxyuridine (BrdU) labeling method was used to identify proliferating cells in the kidney. BrdU (50 mg/kg; Sigma, St. Louis, MO, USA) was intraperitoneally injected into mice, then the mice were sacrificed 1 h later and the kidneys were removed. Cells undergoing DNA synthesis were immunohistochemically identified with monoclonal anti-BrdU antibody (Oncogene Research Products, San Diego, CA, USA) following the manufacturer's protocol. Sections were also treated with DNase 1 (0.33 U/μl) (Roche Applied Science, Mannheim, Germany) at 37 °C for 1 h following digestion with trypsin.

To detect apoptotic cells, the terminal deoxy transferase uridine triphosphate nick end-labeling (TUNEL) method was employed using ApopTag Peroxidase In Situ Apoptosis Detection Kit (Intergen, Purchase, NY, USA) following the manufacturer's protocol. Labeling indices for BrdU labeling and TUNEL were determined by counting labeled nuclei among >1000 nuclei in 10 randomly selected fields under high magnification (400×) for each kidney and values were then averaged.

Statistical analysis. Data are presented as means ± SEM. Statistical analysis was performed by ANOVA, and significance was defined as $P < 0.05$.

Results

Effect of hematopoietic cytokines on BUN and serum creatinine in cisplatin-induced ARF

Subcutaneous administration of cisplatin (15 mg/kg) to mice induced marked increase in BUN and serum

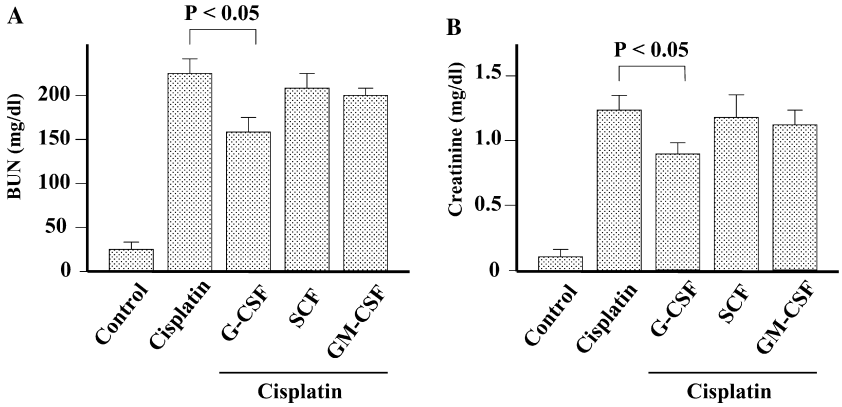

Fig. 1. Effect of hematopoietic cytokines on BUN and serum creatinine in cisplatin-induced ARF. Acute renal injury was induced by subcutaneous administration of cisplatin (15 mg/kg). Mice were injected s.c. with either G-CSF (50 μg/kg), SCF (200 μg/kg), GM-CSF (80 μg/kg), or saline at the time of cisplatin administration and 6, 24, 48, and 72 h after cisplatin administration. Blood samples were collected 96 h after cisplatin administration, then BUN (A) and serum creatinine (B) were measured. Control mice were injected with saline instead of cisplatin and there was no cytokine treatment administered. Data are expressed as means ± SEM.

creatinine (BUN; 221 ± 14 mg/dl, creatinine; 1.25 ± 0.13 mg/dl, $N = 17$) 96 h after cisplatin administration compared with those in control mice injected with saline (BUN; 23 ± 2 mg/dl, creatinine; 0.07 ± 0.02 mg/dl, $N = 5$) (Fig. 1). Treatment with G-CSF significantly ameliorated both BUN and serum creatinine increase induced by cisplatin administration (BUN; 158 ± 12 mg/dl, $P < 0.05$ vs. cisplatin only, creatinine; 0.85 ± 0.14 mg/dl, $P < 0.05$ vs. cisplatin only, $N = 17$). However, there was no significant change observed in BUN or serum creatinine either at 24 h or at 48 h after cisplatin administration by treatment with G-CSF (24 h after cisplatin administration, BUN; 24 ± 1 mg/dl in cisplatin only vs. 22 ± 1 mg/dl in cisplatin and G-CSF, NS, creatinine; 0.08 ± 0.01 mg/dl in cisplatin only vs. 0.07 ± 0.01 mg/dl in cisplatin and G-CSF, NS, $N = 6$ in each group) (48 h after cisplatin administration, BUN; 42 ± 3 mg/dl in cisplatin only vs. 45 ± 2 mg/dl in cisplatin and G-CSF, NS, creatinine; 0.16 ± 0.02 mg/dl in cisplatin only vs. 0.17 ± 0.02 mg/dl in cisplatin and G-CSF, NS, $N = 6$ in each group). There was no significant amelioration observed in BUN or serum creatinine 96 h after cisplatin administration either by treatment with SCF (BUN; 204 ± 16 mg/dl, NS vs.

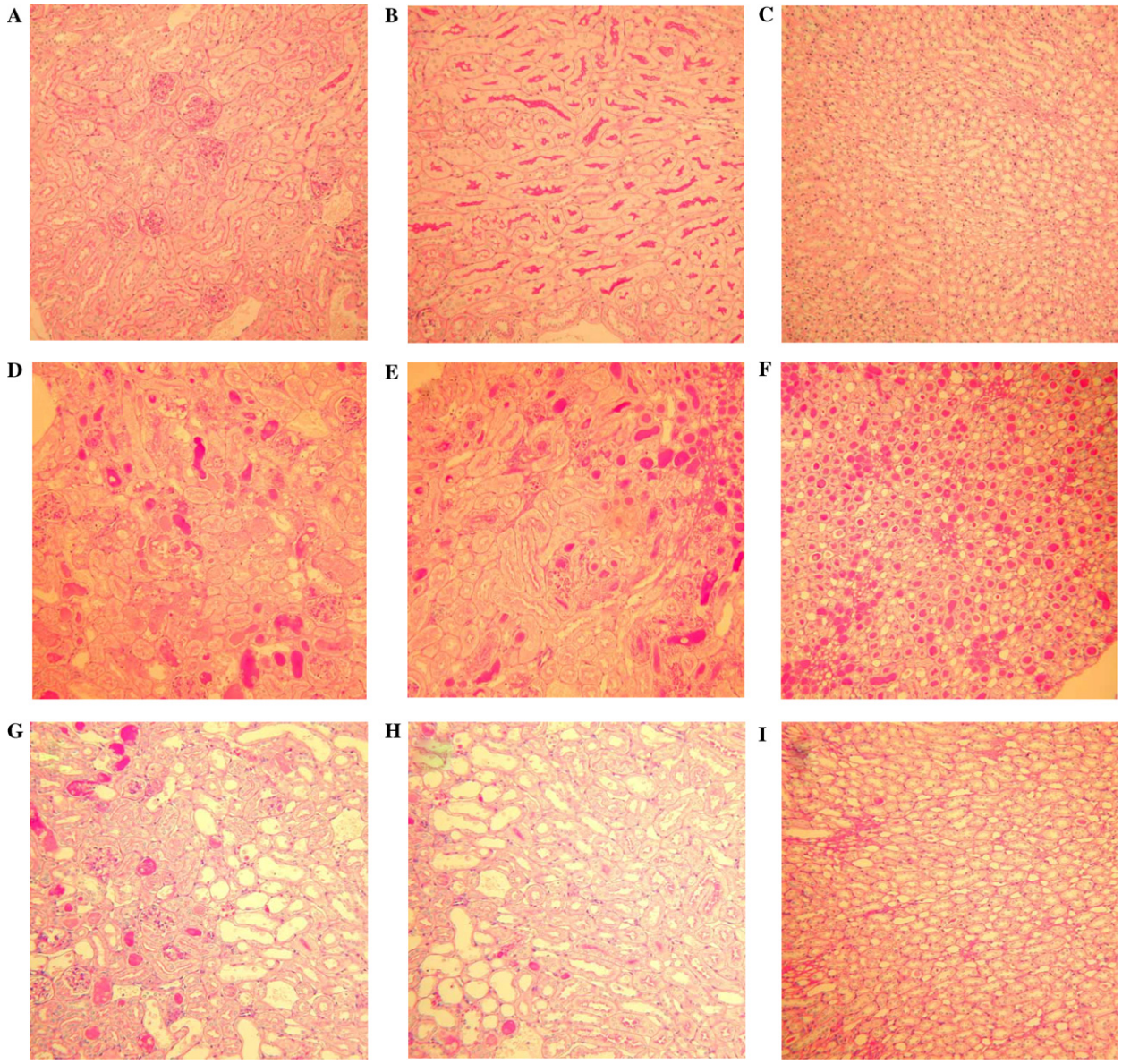

Fig. 2. Histological examination of the kidney. Periodic acid–Schiff (PAS) stained sections of the kidney 96 h after cisplatin administration. (A–C) Control mouse without cisplatin treatment. (D–F) Treated with cisplatin without cytokine treatment. (G–I) Treated with cisplatin and G-CSF. (A,D,G) Cortex. (B,E,H) Outer medulla. (C,F,I) Inner medulla. Administration of cisplatin induced marked necrotic change and subsequent withdrawal of renal tubular cells in the cortex and outer medulla. In the kidneys of mice treated with G-CSF, there were fewer necrotic regions and less withdrawal of renal tubular cells compared with those in mice treated with cisplatin only. Original magnification, 200×.

cisplatin only, creatinine; 1.13 ± 0.20 mg/dl, NS vs. cisplatin only, $N = 8$) or with GM-CSF (BUN; 198 ± 7 mg/dl, NS vs. cisplatin only, creatinine; 1.08 ± 0.15 mg/dl, NS vs. cisplatin only, $N = 8$) (Fig. 1).

Histological study

Administration of cisplatin induced marked necrotic change and subsequent withdrawal of renal tubular cells in the cortex and outer medulla observed in PAS stained sections 96 h after cisplatin administration (Figs. 2A–F). Although these histological changes were also observed in the kidneys of mice treated with both cisplatin and hematopoietic cytokines, there were fewer necrotic regions and less withdrawal of renal tubular cells in the kidneys of mice treated with G-CSF compared with those in mice treated with cisplatin only (Figs. 2G–I). In the kidneys of mice treated with cisplatin and SCF, and in those treated with cisplatin and GM-CSF, the degrees of necrotic change and withdrawal of renal tubules were the same as in those treated with cisplatin only.

Immunohistochemical staining for CD45, CD34, and c-kit revealed that there were only a few CD45-positive cells, CD34-positive cells, and c-kit-positive cells infiltrating to the kidneys of mice treated with cisplatin only. Furthermore, there was no significant change observed in the number of infiltrating CD45-positive, CD34-positive, or c-kit-positive cells in the kidney by treatment with either G-CSF, SCF, or GM-CSF compared with that in those treated with cisplatin only (Figs. 3A–C).

The BrdU labeling index in the kidney was significantly increased by treatment with G-CSF compared with that in those treated with cisplatin only ($0.79 \pm 0.08\%$ vs. $2.43 \pm 0.40\%$, $P < 0.01$, $N = 6$ in each group). There was no significant change observed in the BrdU labeling index by treatment with either SCF ($0.89 \pm 0.13\%$, NS vs. cisplatin only, $N = 6$) or GM-CSF ($0.79 \pm 0.12\%$, NS vs. cisplatin only, $N = 6$) compared with that in those treated with cisplatin only (Figs. 4A, C, and D).

In contrast to the BrdU labeling index, the percentage of TUNEL-positive cells in the kidney was significantly decreased by treatment with G-CSF compared with that in those treated with cisplatin only ($2.44 \pm 0.38\%$ vs. $0.88 \pm 0.21\%$, $P < 0.05$, $N = 6$ in each group). Furthermore, there was no significant change observed in the percentage of TUNEL-positive cells after treatment with either SCF ($1.98 \pm 0.34\%$, NS vs. cisplatin only, $N = 6$) or GM-CSF ($1.91 \pm 0.35\%$, NS vs. cisplatin only, $N = 6$) compared with that in those treated with cisplatin only (Figs. 4B, E, and F). BrdU-positive cells and TUNEL-positive cells were detected only in tubular epithelial regions in all groups, and both the BrdU labeling index and the percentage of TUNEL-positive cells in the kidney of normal mouse were $<0.1\%$.

Effect of G-CSF on serum HGF level and on peripheral blood leukocyte count in cisplatin-induced ARF

Serum HGF level 96 h after cisplatin administration was significantly lower in mice treated with cisplatin and G-CSF compared with that in mice treated with cisplatin only (3.83 ± 0.26 ng/ml in cisplatin only vs. 2.56 ± 0.40 ng/ml in cisplatin and G-CSF, $P < 0.05$, $N = 6$ in each group). There was no significant change observed in peripheral blood total leukocyte count or in peripheral blood granulocyte count 96 h after cisplatin administration by treatment with G-CSF (total leukocyte count; $3840 \pm 117/\mu l$ in cisplatin only vs. $4300 \pm 281/\mu l$ in cisplatin and G-CSF, NS, granulocyte count; $2016 \pm 195/\mu l$ in cisplatin only vs. $2342 \pm 360/\mu l$ in cisplatin and G-CSF, NS, $N = 5$ in each group).

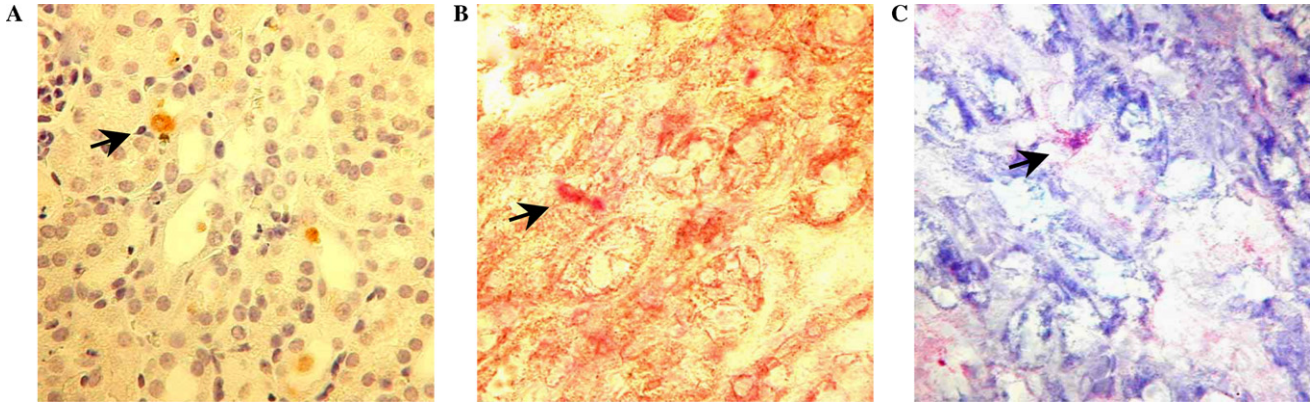

Fig. 3. Immunohistochemical staining of hematopoietic cells in the kidney. Detection of infiltrating CD45-positive cells (A), CD34-positive cells (B), and c-kit-positive cells (C) in the kidneys of mice treated with cisplatin and G-CSF at 96 h after cisplatin administration. There were only a few CD45-positive cells, CD34-positive cells, and c-kit-positive cells infiltrating to the kidney of these mice (arrows). Original magnification, 400×.

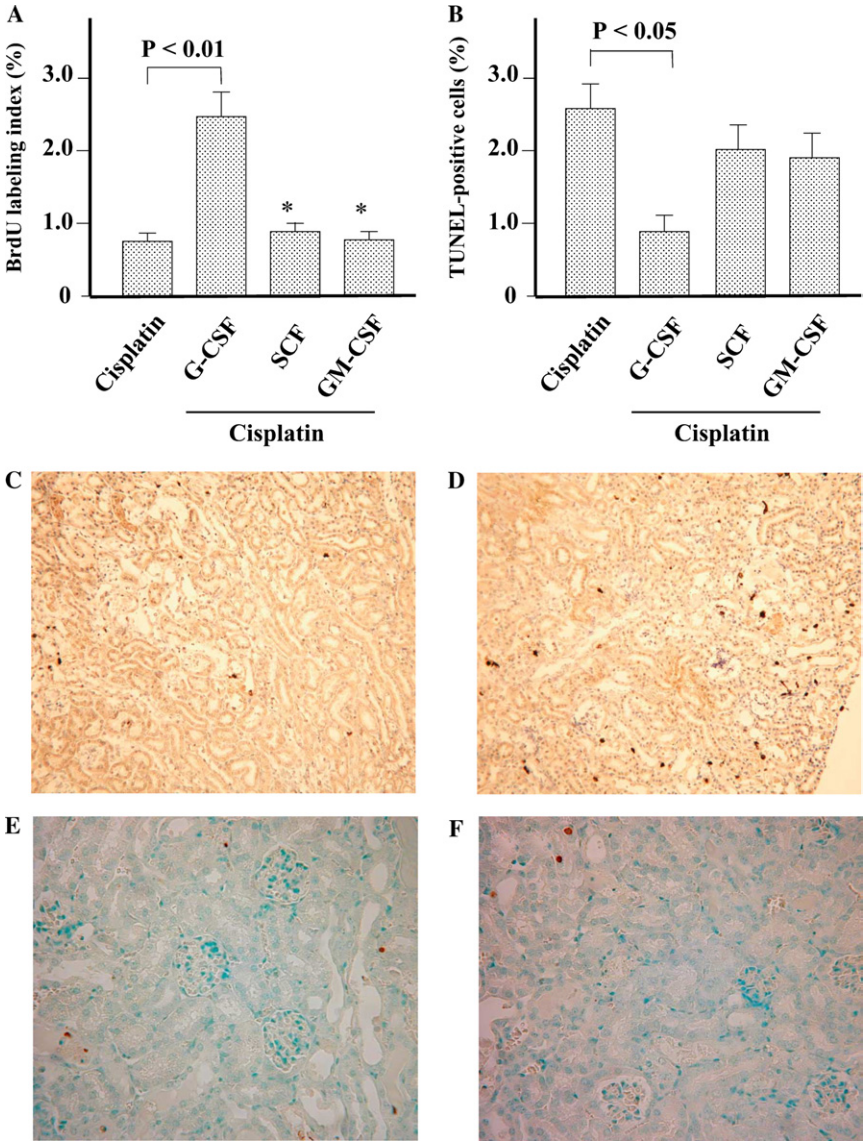

Fig. 4. Effect of hematopoietic cytokines on DNA synthesis and apoptosis of renal tubular cells after cisplatin administration. (A) DNA synthesis assessed by the BrdU labeling index 96 h after cisplatin administration. BrdU (50 mg/kg) was intraperitoneally injected into mice and the mice were sacrificed 1 h later, then the kidneys were removed. (B) Apoptosis assessed by TUNEL 96 h after cisplatin administration. Treatment with G-CSF, but not SCF or GM-CSF, enhanced DNA synthesis and decreased apoptosis of renal tubular cells after cisplatin administration. Data are expressed as means ± SEM. $*P < 0.01$ vs. mice treated with cisplatin and G-CSF. (C,D) Detection of proliferating cells (BrdU-positive cells) in the kidneys of mice treated with cisplatin only (C) and in those from mice treated with cisplatin and G-CSF (D). Original magnification, 200×. (E,F) Detection of apoptotic cells (TUNEL-positive cells) in the kidneys of mice treated with cisplatin only (E) and in those from mice treated with cisplatin and G-CSF (F). Original magnification, 400×.

Discussion

This study shows that the administration of G-CSF, but not SCF or GM-CSF, suppressed the increases in BUN and serum creatinine, and ameliorated necrotic change in acute tubular necrosis induced by cisplatin administration. Although the precise mechanism for how G-CSF, but not SCF or GM-CSF, attenuated histological damage as well as deterioration in renal function induced by cisplatin administration is unclear, our results also indicated that G-CSF acts to suppress the increases in BUN and serum creatinine 96 h after cisplatin administration, but not at 24 h or at 48 h after cisplatin administration, and to accelerate regeneration and prevent apoptosis of renal tubular epithelial cells. These data show that the effect of G-CSF does not result from diminution of toxicity of cisplatin, but from accelerating the recovery from renal injury.

Renal tubular necrosis and apoptosis are morphological changes usually seen in the case of cisplatin-induced renal injury [11,12]. Tubular regeneration is necessary for the recovery of renal morphology and function

following these damages. There seem to be two possible mechanisms to account for the mitogenic and anti-apoptotic effects of G-CSF to tubular epithelial cells observed in our study. One is the direct action of G-CSF on tubular epithelial cells, and the other is the possibility that G-CSF indirectly affects renal tubular cell function via the production of other agents that directly act on renal tubular cells. From this perspective, a recent report [13] showed the elevation of HGF, a potent renotrophic factor with mitogenic and anti-apoptotic activities on renal tubular cells [14–16], in the serum of normal donors for allogeneic peripheral blood stem cell transplantation during G-CSF administration. Thus, we also determined serum HGF levels in our mouse model. However, the serum HGF level was rather significantly decreased in mice treated with cisplatin and G-CSF compared with those treated with cisplatin only. This finding suggests that HGF is not involved in factors leading to attenuated cisplatin-induced renal damage by the G-CSF treatment in our model.

The direct action of G-CSF on renal tubular epithelial cells has not previously been reported. However, stimulating the proliferation of hematopoietic bone marrow stem cells in the bone marrow and mobilization to the peripheral circulation is a well-known action of G-CSF [17]. Furthermore, recent reports indicated that hematopoietic bone marrow stem cells that are mobilized into the circulation play an important role in renal tubular regeneration following ischemically induced acute tubular necrosis, by homing specifically to injured regions of the renal tubule and substantially constituting the majority of cells present in the previously necrotic tubules [8,9]. In contrast to these reports, another report also showed that direct intravenous injection of hematopoietic stem cells did not protect cisplatin-treated mice from renal function deterioration [18]. Thus, we performed immunohistochemical staining for hematopoietic cell marker, i.e., CD45, CD34, and c-kit, to detect hematopoietic cells infiltrating in the kidney. However, there were only a few hematopoietic cells observed in the kidneys of mice treated with cisplatin only, and furthermore, no significant change was observed in the number of hematopoietic cells infiltrating to the kidney by treatment with either G-CSF, SCF, or GM-CSF. This finding suggests that the effect of G-CSF is not due to increased infiltration of hematopoietic cells to the kidney. However, the possibility still exists that some of the regenerated tubular epithelial cells are bone marrow-derived cells, and G-CSF acts to stimulate proliferation for these bone marrow-derived tubular epithelial cells.

A recent report also indicated that hematopoietic stem cell mobilization by treatment with G-CSF severely worsened ischemically induced ARF in mice with a marked increase in peripheral blood leukocyte number and increased granulocyte infiltration to the kidney [19]. However, our data indicated that, by treatment with G-CSF, no significant change was observed in peripheral blood leukocyte number as well as the degree of leukocyte infiltration in the kidney detected by CD45 immunostaining compared with that in those treated with cisplatin only. Thus, in our model, G-CSF seems not to act to worsen ARF via increased peripheral blood leukocyte number and increased leukocyte infiltration to the kidney.

The onset of ARF is often encountered when treating diseases by administration of nephrotoxic drugs or in renal ischemia. Although we used a model of reversible ARF, repeated or continuous insults by these causes may lead to irreversible ARF, for instance, repeated use of antitumoral drugs with a high incidence of nephrotoxicity for the treatment of malignant tumors is often encountered in some clinical settings. Thus, the development of agents that protect renal functions and enhance renal regeneration following renal injury would be of substantial benefit to numerous patients. Further studies are necessary to explore the mechanisms of the renoprotective effect of G-CSF and for its clinical applications. Nevertheless, our result suggests a potential clinical use of G-CSF as a new therapeutic agent following renal injury.

Acknowledgment

This study was supported in part by a Grant-in-Aid for Scientific Research C from the Japan Society for the Promotion of Science.

References

[1] R. Thadhani, M. Pascual, J.V. Bonventre, Acute renal failure, N. Engl. J. Med. 334 (1996) 1448–1460.
[2] D.S. Krause, N.D. Theise, M.I. Collector, O. Henegariu, S. Hwang, R. Gardner, S. Neutzel, S.J. Sharkis, Multi-organ multilineage engraftment by a single bone marrow-derived stem cell, Cell 105 (2001) 369–377.
[3] D.S. Krause, Plasticity of marrow-derived stem cells, Gene Ther. 9 (2002) 754–758.
[4] R. Poulsom, S.J. Forbes, K. Hodivala-Dilke, E. Ryan, S. Wyles, S. Navaratnarasah, R. Jeffery, T. Hunt, M. Alison, T. Cook, C. Pusey, N.A. Wright, Bone marrow contributes to renal parenchymal turnover and regeneration, J. Pathol. 195 (2001) 229–235.
[5] S. Gupta, C. Verfaillie, D. Chmielewski, Y. Kim, M.E. Rosenberg, A role for extrarenal cells in the regeneration following acute renal failure, Kidney Int. 62 (2002) 1285–1290.
[6] M. Nishida, H. Kawakatsu, I. Shiraishi, S. Fujimoto, T. Gotoh, Y. Urata, T. Ono, K. Hamaoka, Renal tubular regeneration by bone marrow-derived cells in a girl after bone marrow transplantation, Am. J. Kidney Dis. 42 (2003) E10–E12.
[7] A. Meguid, E.L. Nahas, Plasticity of kidney cells: role in kidney remodeling and scarring, Kidney Int. 64 (2003) 1553–1563.
[8] F. Lin, K. Cordes, L. Li, L. Hood, W.G. Couser, S.J. Shankland, P. Igarashi, Hematopoietic stem cells contribute to

the regeneration of renal tubules after renal ischemia-reperfusion injury in mice, J. Am. Soc. Nephrol. 14 (2003) 1188–1199.
[9] S. Kale, A. Karihaloo, P.R. Clark, M. Kashgarian, D.S. Krause, L.G. Cantley, Bone marrow stem cells contribute to repair of the ischemically injured renal tubule, J. Clin. Invest. 112 (2003) 42–49.
[10] R. Safirstein, J. Winston, M. Goldstein, D. Moel, S. Dikman, J. Guttenplan, Cisplatin nephrotoxicity, Am. J. Kidney Dis. VIII (1986) 356–367.
[11] W. Lieberthal, V. Triaca, J. Levine, Mechanisms of death induced by cisplatin in proximal tubular epithelial cells: apoptosis vs. necrosis, Am. J. Physiol. 270 (1996) F700–F708.
[12] H. Zhou, T. Miyaji, A. Kato, Y. Fujigaki, K. Sano, A. Hishida, Attenuation of cisplatin-induced acute renal failure is associated with less apoptotic cell death, J. Lab. Clin. Med. 134 (1999) 649–658.
[13] K. Fujii, F. Ishimaru, T. Kozuka, K. Matsuo, K. Nakase, I. Kataoka, T. Tabayashi, K. Shinagawa, K. Ikeda, M. Harada, M. Tanimoto, Elevation of serum hepatocyte growth factor during granulocyte colony-stimulating factor-induced peripheral blood stem cell mobilization, Br. J. Haematol. 124 (2004) 190–194.
[14] K. Kawaida, K. Matsumoto, H. Shimazu, T. Nakamura, Hepatocyte growth factor prevents acute renal failure and accelerates renal regeneration in mice, Proc. Natl. Acad. Sci. USA 91 (1994) 4357–4361.
[15] Y. Liu, A.M. Sun, L.D. Dworkin, Hepatocyte growth factor protects renal epithelial cells from apoptotic cell death, Biochem. Biophys. Res. Commun. 246 (1998) 821–826.
[16] Y. Liu, Hepatocyte growth factor promotes renal epithelial cell survival by dual mechanisms, Am. J. Physiol. 277 (1999) F624–F633.
[17] J. Thomas, F. Liu, D.C. Link, Mechanisms of mobilization of hematopoietic progenitors with granulocyte colony-stimulating factor, Curr. Opin. Hematol. 9 (2002) 183–189.
[18] M. Morigi, B. Imberti, C. Zoja, D. Corna, S. Tomasoni, M. Abbate, D. Rottoli, S. Angioletti, A. Benigni, N. Perico, M. Alison, G. Remuzzi, Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure, J. Am. Soc. Nephrol. 15 (2004) 1794–1804.
[19] F. Tögel, J. Isaac, C. Westenfelder, Hematopoietic stem cell mobilization-associated granulocytosis severely worsens acute renal failure, J. Am. Soc. Nephrol. 15 (2004) 1261–1267.