Kidney International, Vol. 60 (2001), pp. 167–172

Role of stem cell factor and mast cells in the progression of chronic glomerulonephritides[1]

Ahmed F. El-Koraie, Nahed M. Baddour, Ahmed G. Adam, Essam H. El Kashef, and A. Meguid El Nahas

Sheffield Kidney Institute, Northern General Hospital Trust, Sheffield, England, United Kingdom, and University of Alexandria, Alexandria, Egypt

Role of stem cell factor and mast cells in the progression of chronic glomerulonephritides.

Background. Mast cells (MCs) have been implicated in the pathogenesis of atherosclerosis and tissue fibrosis. However, the role of MC in the development of renal fibrosis has not been fully elucidated. Stem cell factor (SCF; the ligand for MC c-kit receptor) is thought to attract and activate MCs.

Methods. The intensity of MC infiltration and SCF expression in renal biopsies from 56 patients with different forms of primary and secondary glomerulonephritis and five controls were investigated by immunohistochemistry, using a monoclonal anti-human MC tryptase antibody and a polyclonal anti-human SCF antibody.

Results. A large number of MCs were detected in the renal interstitium of the diseased kidneys. Immunostainable SCF was detected in tubular as well as interstitial cells. MC infiltration was significantly higher in glomerulonephritis (16.9 ± 10.2 cells/field) compared with controls (2.8 ± 2.1 cells/field, $P = 0.03$). Similarly, immunostainable SCF was 0.6 ± 0.3% for controls and 3.3 ± 2.1% in the glomerulonephritis group ($P = 0.02$). MC infiltration was highly correlated with SCF expression in diseased kidneys ($r = 0.93$, $P = 0.0001$). Double immunostain showed them to colocalize in some interstitial cells. Analysis of MC proliferation [proliferating cell nuclear antigen (PCNA) positivity] and apoptosis (in situ end labeling of DNA) showed these cells to be terminally differentiated. Both MCs and SCF were correlated with interstitial fibrosis (R = 0.71 for MC and R = 0.62 for SCF, $P = 0.0001$) and interstitial α-smooth muscle actin (R = 0.69 for MC and R = 0.60 for SCF $P = 0.0001$). Using regression analysis, the number of MC infiltration was found to be a very powerful determinant of interstitial fibrosis in the glomerulonephritis group ($R^2 = 91.4\%$).

Conclusion. MCs as an infiltrating hematopoietic cell and its growth factor (SCF) seem to be up-regulated in glomerulonephritis, and may play a role in the development of renal fibrosis.

[1] **See Editorial by Eddy, p. 375**

Key words: Schistosoma nephropathy, myofibroblasts, glomerulosclerosis, interstitial fibrosis, atherosclerosis, renal fibrosis, chronic renal failure.

Received for publication May 26, 2000
and in revised form January 18, 2001
Accepted for publication February 20, 2001

The progression of chronic renal failure (CRF) is characterized by numerous common pathways leading to glomerulosclerosis (GS) and tubulointerstitial fibrosis [1]. The role of infiltrating inflammatory cells in the initiation and progression of these scarring processes is becoming increasingly recognized [2]. A wide range of inflammatory cells, including lymphocytes and monocytes, has been implicated [2]. Furthermore, close correlations have been demonstrated between the severity of the interstitial inflammatory infiltrate and the renal prognosis [3]. Interactions are thought to take place between these infiltrating cells and resident glomerular and interstitial renal cells, leading to the initiation and progression of GS and tubulointerstitial fibrosis, respectively [1, 3].

Mast cells (MCs) have been implicated in tissue fibrosis, atherosclerosis, as well as tissue reaction to tumors [4, 5]. Preliminary reports suggest a role for MCs in the pathogenesis of renal inflammation and scarring [6]. MCs have the capacity to secrete cytokines and growth factors capable of generating positive feedback loops of inflammation and fibrosis [7].

Mast cells are bone marrow–derived hematopoietic cells that share phenotypic characteristics with monocytes/macrophages [8]. Once in the tissue, these cells differentiate and proliferate under the influence of the local microenvironment [9]. This may depend on interactions between MCs and other leukocytes as well as tissue fibroblasts [10]. Fibroblasts are known to secrete a wide range of growth factors, including stem cell factor (SCF), which acts on MCs through its c-kit receptor [11].

Stem cell factor, also known as MC growth factor, steel factor, or kit ligand, is essential for MC development [12] and was shown to be a major MC agonist under both physiologic and pathologic conditions, leading to MC chemotaxis, adhesion, activation, proliferation, and viability [13].

The progression of glomerulonephritis is associated with the progression of the primary glomerulopathy to sclerosis as well as marked tubulointerstitial scarring.

Table 1. Clinical data of patients and controls

Variable	Patients ($n = 56$)	Controls ($n = 5$)
Age *years*	29.6 ± 17.3	43.1 ± 12.4
Serum urea *mg/dL*	122.1 ± 90.4	28.1 ± 14.1
Serum creatinine *mg/dL*	4.9 ± 4.5	1.1 ± 0.3
MAP *mm Hg*	108.7 ± 18.5	95.8 ± 6.1
Proteinuria *g/24 h*	1.8 ± 2.4	0

Data are mean ± SD. Abbreviation is MAP, mean arterial pressure.

The progression of CRF in these patients is often correlated with the severity of the tubulointerstitial changes [14]. Increasing evidence suggests that the processes of GS and tubulointerstitial fibrosis share common pathways, including inflammatory cell infiltration, fibroblasts/myofibroblasts proliferation, and excessive deposition of extracellular matrix [1].

With this in mind, we sought to determine the presence and relevance of MCs and their growth factor (SCF) to renal scarring in a wide range of nephropathies. We also attempted to identify the relationship of MCs and SCF to renal fibroblasts/myofibroblasts as well as tissue fibrosis.

METHODS

Patients

We retrospectively studied renal biopsy archival material from 56 patients with mixed primary ($N = 18$) and secondary ($N = 38$) glomerulonephritis. The secondary glomerulonephritides included 16 patients with schistosomal nephropathy, 6 patients with systemic lupus erythematosus (SLE), 5 patients with anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis, 4 with secondary membranous glomerulonephritis (2 of them after drugs and 2 had bronchogenic carcinoma), 3 with poststreptococcal glomerulonephritis, 3 with amyloidosis, and 1 with Alport syndrome. For control purposes, our study included the sections from the healthy pole of nephrectomy specimens ($N = 5$, removed for hypernephroma). The clinical characteristics of the groups studied are given in Table 1.

Immunohistochemistry

Renal biopsies were fixed in 10% neutral-buffered formalin, paraffin-embedded, sectioned at 4 μm, and stained using a standard avidin-biotin-peroxidase complex (ABC) technique. Briefly, sections were deparaffinized and rehydrated in descending grades of alcohol. Following blocking of endogenous peroxidase activity with 3% H_2O_2 in methanol and nonspecific binding sites with a protein blocker, the primary antibody was added in the following concentrations: anti-MC tryptase (MCT) 1:150, anti-SCF 1:100, anti–c-kit (CD117) 1:50, and anti-proliferating cell nuclear antigen (PCNA) 1:50, with overnight incubation at 4°C. For PCNA, antigen-revealing techniques were performed in the form of microwave treatment of sections in Tuf solution (Signet, Glasgow, UK) for 1 minute, whereas for MCT, the sections were trypsinized for 10 minutes in 37°C. The following day, the biotinylated secondary antibody (Vector Laboratories, Peterborough, UK) was added at a concentration of 5% for 30 minutes followed by addition of the ABC (Vector Laboratories). Visualization of the reaction was performed using 3 amino-ethyl-9-carbazole (AEC; Vector Laboratories) as the chromogen. All steps were performed at room temperature (RT) in a humidity chamber unless otherwise specified. Antigen-revealing techniques were used with trypsin 0.1% for 20 minutes at RT for MC tryptase. Controls included incubation of sections in the absence of the primary antibody or with nonimmune appropriate gamma globulins.

The primary antibodies used were monoclonal anti-human MC tryptase antibody (Dako, Ely, UK) [15], monoclonal anti-human α-smooth muscle actin antibody (α-SMA; Dako) [16], monoclonal anti-CD68 (PG-M1, monocyte/macrophage; Dako) [17], polyclonal rabbit anti-human c-kit (CD117; Dako) [18], polyclonal goat anti-human SCF antibody (Santa Cruz, Santa Cruz, CA, USA) [19], and monoclonal antiproliferating cell nuclear antigen (PCNA, PC 10) clone (Dako) [20].

Double immunostaining

Double immunohistochemical staining was performed on paraffin sections for MC tryptase, α-SMA, and CD68 with SCF. This was aimed to determine the possible associations between these cells (MCs, myofibroblasts, and monocytes/macrophages) and SCF. Briefly, 4 μm sections were dewaxed and hydrated. Sections were processed as described previously in this article for SCF. Afterward, they were preincubated with blocking (horse) serum for 30 minutes, labeled with the antitryptase, α-SMA, or CD68 antibody at 37°C for one hour. Sections were labeled with biotinylated secondary anti-mouse [in a 5% phosphate-buffered saline (PBS)/normal rat serum solution] at 37°C for 30 minutes and then incubated with ABC compound for 30 minutes at 37°C. 3,3′ Diaminobenzidine tetrahydrochloride (DAB) was used as the chromogen. Control sections were incubated with nonimmune normal rat serum (at a comparative protein concentration). Positive staining was seen as a brownish cytoplasmic deposit. Intervening washes were performed with 0.1% nonionic detergent in PBS.

Double staining for PCNA and apoptosis was performed on MC-stained sections. This was aimed to determine the fate of these cells in renal tissues.

In situ end labeling/apoptosis staining

Apoptosis was detected by the in situ end labeling (ISEL) of fragmented DNA using a commercial Apo-

Table 2. Histopathologic diagnoses of the studied groups

Pathologic diagnosis	Number (*percent of total*)
Mesangiocapillary glomerulonephritis (MCGN)	31 (55)
Membranous nephropathy (MN)	4 (7)
Mesangioproliferative glomerulonephritis (MPGN)	7 (12.5)
Focal and segmental glomerulosclerosis (FSGS)	5 (9)
Amyloidosis	3 (5.5)
End-stage renal disease (ESRD)	6 (11)

A total of 56 patients were studied.

Table 3. Immunohistochemical scores for interstitial mast cells (MC) and stem cell factor (SCF) in the two studied groups

Marker	Patients ($n = 56$)	Controls ($n = 5$)	*P* value
MC/HPF	16.9 ± 10.19	2.8 ± 2.1	0.023
SCF %	3.3 ± 2.1	0.6 ± 0.3	0.020

HPF is high power field.
Data are mean ± SD.

ptag kit (Intergen, Purchase, NY, USA) [21]. Briefly, sections were deparaffinized and stripped of proteins by incubation with proteinase K (Sigma, Poole, Dorset, UK) in PBS at RT for 15 minutes. Following washing in distilled water, endogenous peroxidase activity was quenched by 3% H_2O_2 for five minutes. After incubation with the equilibration buffer, the samples were incubated with terminal deoxyribonucleotidyl transferase (TdT) in reaction buffer (containing digoxigenin-labeled nucleotide) at 37°C for 60 minutes. The reaction was terminated using a stop buffer. Following rinsing with PBS, the tissue sections were covered with antidigoxigenin peroxidaser for 30 minutes at RT, washed in PBS, stained with DAB, and counterstained with hematoxylin.

Morphometric analysis

All the morphologic evaluations were performed by two of the authors (A.F. and N.B.) blinded to the experimental code. A standard point-counting method was used to quantitate Masson trichrome stain for estimation of both glomerular sclerosis (GS) and interstitial fibrosis (IF) and for counting the percentage of SCF positivity as well under a magnification of ×400 [22]. For that, 12 consecutive nonoverlapping fields were evaluated in quantitation of the interstitium. A total of 81 × 12 points was evaluated in each biopsy. All available glomeruli in the biopsy were point counted. All positively staining points falling on the grid's cross-points were counted. The result was expressed as the percentage of stained points of the total number of points counted. The mean score per biopsy was calculated.

To quantitate the amount of MCs (tryptase + cells) in both glomerular and tubulointerstitial compartments, 12 fields in the cortical areas of each kidney were examined at a magnification of ×400 with a Reichert microscope. All available glomeruli in the biopsy were screened for positive cells as well. During evaluation of the interstitial areas, fields containing glomerular parts were ignored.

We confirmed the nature of MC by additional staining of the paraffin-embedded sections with toluidine blue, a well-established histologic stain to identify MCs [15].

Semiquantitative histomorphometric analysis

This was performed with the following parameters evaluated according to an arbitrary score (from 0 to +3) as previously described [22]: glomerular mesangial hypercellularity, GS, tubular atrophy, interstitial cellular infiltration, IF, and vascular hyalinosis.

Statistical analysis

The results are expressed as mean ± SD. The significance of differences between the clinical groups was determined by Kruskall-Wallis followed by Mann-Whitney U Wilcoxon Rank sum test for post hoc comparisons. Correlations between the different parameters were performed using the Spearman's rank correlation test. Simple regression analysis using a computer-based program (SPSS) was performed. The coefficient of determination (R^2) is expressed as a percentage. A *P* value of $< 5\%$ was considered significant.

RESULTS

Clinical findings

The majority (60%) of patients studied had impaired renal function (serum creatinine >1.5 mg/dL). A significant proportion (96%) had proteinuria (>300 mg/24 hours). Seventy-eight percent of the patients had a significant grade of proteinuria (greater that 1 g/24 hours). Hypertension, often treated, was present in 67% of patients. Control patients had normal serum creatinine at the time of the nephrectomy. None was known to have proteinuria or hypertension. The clinical profile of the patient is detailed in Table 1.

Histopathological diagnosis

This histologic evaluation and description of the glomerular and tubulointerstitial parameters of the renal biopsies are described in Table 2. Histologically, the pole of the nephrectomy specimens used for the analysis was normal.

Mast cell (tryptase + cells) expression

The two methods used for the detection of MC, namely, immunostaining for MCT and toluidine blue, were concordant (Fig. 1). Very few MCs were detected in the interstitium of normal kidneys. In contrast, many MCs were detected in periglomerular areas as well as in large numbers in the renal interstitium of diseased kidneys (Table 3 and Fig. 2 A, B). The distribution of MC

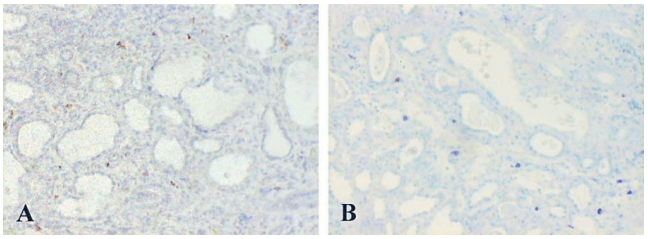

Fig. 1. (*A*) Photomicrograph showing the immunostain for mast cell tryptase (MCT) in a diseased cell (×200). (*B*) Photomicrograph showing mast cells (MC) in the interstitium of a diseased kidney stained with toluidine blue (×200).

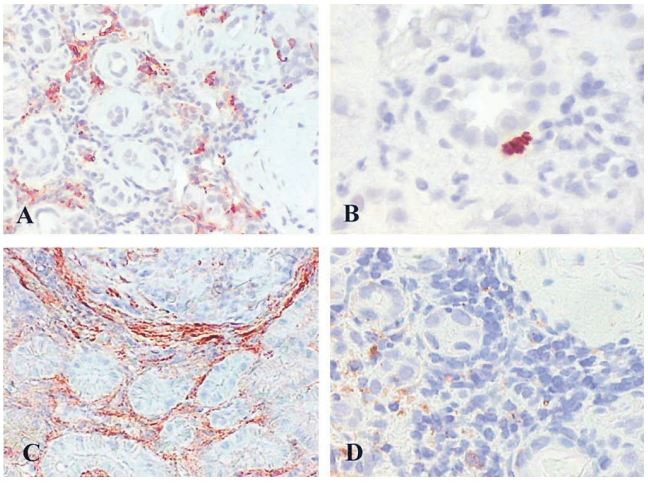

Fig. 2. (*A*) Photomicrograph showing MCT+ cells in the renal interstitium. (*B*) Periglomerular distribution of MC (×400). (*C*) Distribution of α-smooth muscle actin (α-SMA) + cells in a diseased kidney (×200). (*D*) CD68+ cells among interstitial infiltrates (×200).

was mainly cortical with few medullary infiltrating cells. This distribution was similar to that of α-SMA–positive myofibroblasts (Fig. 2C). The intensity of the distribution of MC varied, although this was always in a sporadic rather than a clustered manner, unlike CD68-positive macrophages that were invariably included in areas of heavy inflammatory interstitial infiltrations (Fig. 2D). No significant difference in the distribution pattern of MC was observed between different nephropathies. Double immunostaining of tryptase + cells for PCNA and their ISEL failed to show any proliferating or apoptotic MCs.

Stem cell factor expression

Stem cell factor was detectable in few normal kidneys within the interstitial area. In diseased kidneys, SCF expression was located in a few glomerular parietal epithelial cells (Fig. 3A). In addition, SCF immunostain was detectable in the tubulointerstitium (tubular cells, fibroblasts, peritubular capillaries, and the renal interstitium; Fig. 3 B, C). There was significantly more immunoreactive SCF in diseased kidneys compared with controls (Table 3).

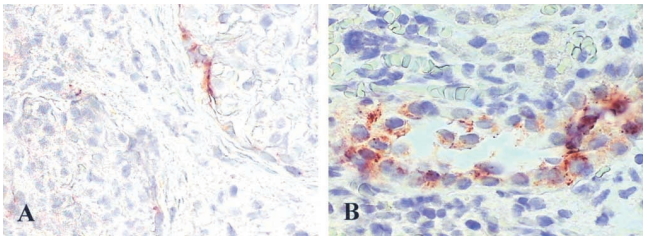

Fig. 3. (*A*) Photomicrograph showing immunostaining for stem cell factor (SCF) within a glomerular parietal epithelial cell of a diseased kidney (×400). (*B*) Immunostaining for SCF within tubular cells of a diseased kidney (×400).

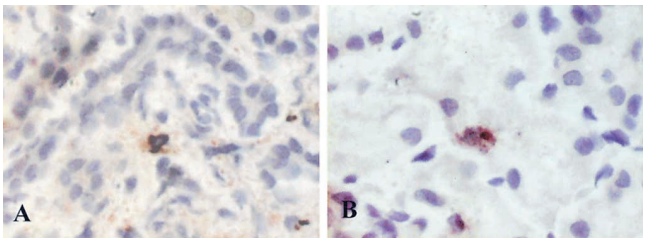

Fig. 4. (*A*) Photomicrograph showing double staining (brown color) for SCF and CD68+ macrophages within an interstitial cell in a diseased kidney (×400). (*B*) Double staining (brown color) for SCF and MCT within an interstitial cell in a diseased kidney (×400).

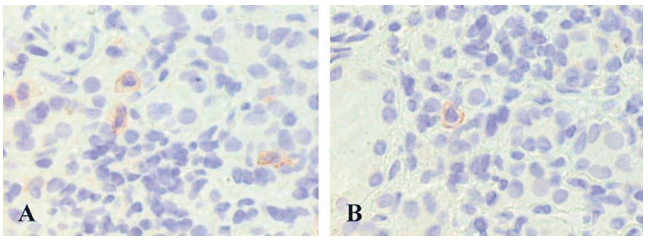

Fig. 5. (*A*) Photomicrograph showing few interstitial cells stained for C-kit in a diseased kidney (×400). (*B*) Photomicrograph showing an interstitial cell stained for C-kit with a membrane-bound pattern of immunostaining (×400).

No significant difference in the distribution pattern of SCF was observed between different nephropathies.

There was a very highly positive correlation between the number of MCs and the intensity of SCF immunostaining in the nephropathy group (Table 4). On the other hand, a weaker correlation was noted between the overall severity of interstitial inflammation and SCF immunostaining ($r = 0.314$, $P = 0.048$).

Double immunostain showed SCF to colocalize with both interstitial monocytes/macrophages (CD68-positive cells) as well as MCs (tryptase-positive cells; Fig. 4).

The SCF receptor (c-kit) was detected in a few interstitial cells (Fig. 5A). The distribution of the immunostain was very suggestive of a membrane-associated receptor (Fig. 5B).

Table 4. Correlation between the studied parameters

	MC (interstitial)		SCF (interstitial)	
Diagnosis	*r*	*P*	*r*	*P*
Glomerulosclerosis	0.59	0.001	0.53	0.001
Interstitial fibrosis	0.71	0.0001	0.62	0.001
α-SMA	0.69	0.0001	0.60	0.001
SCF	0.93	0.0001	1	

Abbreviations are: α-SMA, α-smooth muscle actin; SCF, stem cell factor. *r*, coefficient of correlation; *P*, level of significance.

Correlations between the studied parameters

There was a strong positive correlation between the severity of GS and both the number of interstitial MCs and immunostainable SCF in diseased kidneys (Table 4). Furthermore, both the number of interstitial MCs and the distribution of interstitial SCF immunostain were very strongly correlated with the severity of interstitial fibrosis (Table 4). The number of interstitial MCs was found to be powerful determinants of IF in diseased kidneys. This predictive power exceeded that of any other parameter, including the number of interstitial myofibroblasts, as the coefficient of determination (R^2) for MCs was 91%, whereas that of interstitial α-SMA + cells was only 67%. In addition, there was a strong correlation between the extent of SCF immunostaining and the degree of tubular atrophy ($r = 0.626$, $P < 0.0001$). On the other hand, there was no correlation between SCF immunostain and proteinuria.

DISCUSSION

Our study shows that scarred human kidneys are associated with a significant infiltration of the interstitium with MCs. Using an antitryptase antibody, these have been identified in areas of interstitial fibrosis in association with myofibroblasts. This method has been validated by others and found to be reliable for the detection of these cells in paraffin sections [15]. Also, the MCs were stained by toluidine blue, which showed essentially the same distribution of the tryptase-positive MC. Our data confirm previous observations of the association between MCs and inflammatory as well as fibrotic diseases. A role has been attributed to these hematopoietic cells in tissue fibrosis, including that following experimental myocardial ischemia [23]. In ischemic hearts as in our kidney sections, these cells accumulate in areas of fibrosis and collagen deposition [23]. MCs have been associated with acute cellular rejection of human renal allografts and the ensuing renal fibrosis [24]. They have also been detected in the kidneys of patients with chronic IgA nephropathy where they seemed to influence the progression of the disease [25]. In that study, patients with a high number of interstitial MCs had severe interstitial fibrosis and progressive nephropathy [25].

Mast cells have been implicated in the pathogenesis of fibrosis, as they are capable of releasing a wide range of fibrogenic factors and growth factors [26], including histamine, tryptase, as well as transforming growth factor-β (TGF-β) and basic fibroblast growth factor (bFGF) [27]. Histamine is a potent stimulator of fibroblast proliferation and collagen synthesis [28]. Tryptase, on the other hand, is chemotactic as well as mitogenic for fibroblasts [29]. TGF-β is thought to be one of the most potent renal fibrogenic growth factors [30]. The proximity of MCs and myofibroblasts in kidney sections suggests that there are close interactions between these cells within the renal interstitium. MCs are likely to be key players in the pathogenesis of IF as previously suggested in renal allografts [24] and IgA nephropathy [25]. This is supported in our study by the close correlations between the number of interstitial MC and the severity of IF. The power of MC to determine the severity of such a fibrosis exceeded that of interstitial inflammatory infiltrate as well as that of myofibroblasts. Until now the latter were thought to be one of the most powerful predictors of IF in human renal biopsies [22, 31].

For the first time, to our knowledge, we also detected SCF in human kidneys. While barely detectable in normal kidneys, there was a marked up-regulation of its immunostain in diseased kidneys. SCF distribution was both cellular and interstitial. It appeared to localize in areas of interstitial expansion and fibrosis, and was detectable primarily in tubular cells and in interstitial infiltrating cells. Whether these cells produce SCF and attract MCs to the interstitium remains to be determined. Of interest, some have attributed similarities between MCs and marrow-derived monocytic cells [32]. In the interstitium, SCF appears to be associated with a variety of cells. The observed association of SCF around and within MC confirms the role of this factor in the attraction, activation, and proliferation of MCs [13]. MCs are known to have cell surface receptors for this growth factor [11]. Our study identifies the presence of the SCF receptor, c-kit, in a few interstitial cells. A cell surface distribution was suggested from the immunostaining pattern. It has previously been established that this cell surface receptor is unique to tissue MCs [17]. The fact that there are fewer cells staining for the SCF receptor (c-kit) can be explained, as previously suggested [33], by a decrease in the number of c-kit–positive cells caused by probable occupation of the receptor by the SCF or its down-regulation and internalization after ligand-receptor interaction [33]. SCF immunostain was also observed in interstitial monocytes, known to produce and release SCF [34]. Furthermore, a few myofibroblasts appeared to double stain for SCF, suggesting interactions between these cells and MCs. Some tubular cells appeared to stain for SCF. Furthermore, there was a close correlation between the severity of tubular atrophy and the immunostaining for

SCF, suggesting an association. Whether atrophic or injured tubular cells produce and release SCF is unknown. Activated tubular cells have been shown to release a wide range of cytokines, chemokines, and growth factors [35].

The association of MCs, monocytes, myofibroblasts, and SCF within human kidney biopsies suggests a very potent fibrogenic environment. It is likely that the interactions between these cells are facilitated by the release and action of SCF. However, this is most probably one of many growth factors released by these cells that may be involved in these inflammatory and fibrogenic interactions within diseased kidneys.

In conclusion, we show that MCs and their associated growth factor (SCF) and its receptor (c-kit) are present within the interstitium of scarred human kidneys. We postulate that they play a role in the initiation and progression of renal IF. However, confirmation of such a hypothesis and the precise mechanisms involved remain to be determined by further studies.

Reprint requests to A. Meguid El Nahas, M.D., Sheffield Kidney Institute, Northern General Hospital Trust, Herries Road, Sheffield S5 7AU, England, United Kingdom.
E-mail: m.el-nahas@sheffield.ac.uk

REFERENCES

1. El Nahas AM: Glomerulosclerosis: Intrinsic and extrinsic pathways. *Nephrol Dial Transplant* 11:773–777, 1996
2. Boucher A, Droz D, Adafer E, Noel LH: Characterization of mononuclear cell subsets in renal cellular interstitial infiltrates. *Kidney Int* 29:1043–1049, 1986
3. Alexopoulos E, Seron D, Hartley RB, Cameron JS: The role of interstitial infiltrates in IgA nephropathy: A study with monoclonal antibodies. *Nephrol Dial Transplant* 4:187–195, 1989
4. Thompson HL, Burbelo PD, Gabriel G, *et al:* Murine mast cells synthesize basement membrane components: A potential role in early fibrosis. *J Clin Invest* 87:619–623, 1991
5. Ruger H, Dunbar PR, Hasan O, *et al:* Human mast cells produce type VIII collagen in vivo. *Int J Exp Pathol* 75:397–404, 1994
6. Yoshimura A, Mori W: Renal tissue mast cells in liver diseases. *Int Urol Nephrol* 23:511–515, 1991
7. Gordon JR, Burd PR, Galli SJ: Mast cells as a source of multifunctional cytokines. *Immunol Today* 11:458–464, 1990
8. Horny HP, Ruck P, Xiao JC, Kaisering E: Immunoreactivity of normal and neoplastic human tissue mast cells with macrophage-associated antibodies, with special reference to the recently developed antibody PG-M1. *Hum Pathol* 24:335–338, 1993
9. Galli SJ: New insights into "the riddle of the mast cells": Microenvironmental regulation of mast cell develoment and phenotypic heterogeneity. *Lab Invest* 62:5–33, 1990
10. Toth T, Toth-Jakatics R, Jimi S, *et al:* Mast cells in rapidly progressive glomerulonephritis. *J Am Soc Nephrol* 10:1498–1505, 1999
11. Brito JM, Borojevic R: Liver granulomas in schistosomiasis: Mast cell dependent induction of SCF expression in hepatic stellate cells is mediated by TNF-α. *J Leukoc Biol* 62:389–395, 1997
12. Valent P: The riddle of the mast cell: Kit (cd117) ligand as the missing link. *Immunol Today* 15:111–114, 1994
13. Nilsson G, Butterfield JH, Nilsson K, Siegbaha A: Stem cell factor is chemotactic for human mast cells. *J Immunol* 1533:3718–3723, 1994
14. D'Amico G, Ferrario F, Rastaldi MP: Tubulointerstitial damage in glomerular disease: Its role in the progression or renal damage. *Am J Kidney Dis* 26:124–132, 1995
15. Walls AF, Bennett AR, McBride HM, *et al:* Production and characterization of monoclonal antibodies specific for mast cell tryptase. *Clin Exp Allergy* 20:581–589, 1990
16. Skalli O, Ropraz P, Trzeciak A, *et al:* A monoclonal antibody against α-smooth muscle actin: A new probe for smooth cell differentiation. *J Cell Biol* 103:2787–2796, 1986
17. Falini B, Flenghi L, Pileri S, *et al:* PG-M1, a new monoclonal antibody directed against a fixative-resistant epitope on the macrophage restricted form of the CD68 molecule. *Am J Pathol* 142:1359–1372, 1993
18. Tsuura Y, Hiraki H, Watanabe K, *et al:* Preferential localization of c-kit product in tissue mast cells, basal cells of skin, epithelial cells of breast, small cell lung carcinoma and seminoma/dysgerminoma in human: Immunohistochemical study of formalin-fixed, paraffin-embedded tissues. *Virchows Arch* 424:135–141, 1994
19. Galli SJ, Zsebo KM, Geissler EN: The kit ligand, stem cell factor. *Adv Immunol* 55:1–96, 1991
20. Waseem NH, Lane PP: Monoclonal antibody analysis of the proliferating cell nuclear antigen (PCNA): Structural conservation and the detection of a nucleolar form. *J Cell Sci* 96:121–129, 1990
21. Zhang G, Oldroyd S, Huang LH, *et al:* Role of apoptosis in the development of tubulointerstitial fibrosis during experimental obstructive nephropathy. *Exp Nephrol* 9:71–80, 2001
22. Goumenos D, Brown CB, Shortland J, El Nahas AM: The myofibroblast, predictor of progression in IgA nephropathy. *Nephrol Dial Transplant* 9:1418–1425, 1994
23. Bankl HC, Radaszkiewicz T, Klappacher G: Increase and redistribution of cardiac mast cells in auricular thrombosis: Possible role of kit ligand. *Circulation* 91:275–283, 1995
24. Lajoie GL, Nadasdy T, Laszik Z, *et al:* Mast cells in acute cellular rejection of human allografts. *Mod Pathol* 9:1118–1125, 1996
25. Ehara T, Shigimatsu H: Contribution of mast cells to tubulointerstitial lesions in IgA nephritis. *Kidney Int* 54:1675–1683, 1998
26. Bradding P, Feather LH, Wilson S, *et al:* Immunolocalization of cytokines in the nasal mucosa of normal and perineurial rhinitic subjects: The mast cell as a source of IL-4, IL-5, and IL-6 in human allergic mucosal inflammation. *J Immunol* 151:3853–3865, 1993
27. Qu Z, Lieblex JM, Poevers MR, *et al:* Mast cells are a major source of basic fibroblast growth factor in chronic inflammation and cutaneous hemangioma. *Am J Pathol* 147:564–573, 1995
28. Hatamochi A, Fujiwara K, Veki H: Effects of histamine on collagen synthesis by cultured fibroblasts derived from guinea pig skin. *Arch Dermatol Res* 277:60–64, 1985
29. Ruoss SJ, Hartmann T, Caughey GH: Mast cell tryptase is a mitogen for cultured fibroblasts. *J Clin Invest* 88:493–499, 1991
30. Desmouliere A, Geinoz A, Gabbiani F, Gabbiani G: Transforming growth factor β1 induces α-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing fibroblasts. *J Clin Biol* 122:1103–1111, 1993
31. Essawy M, Soleymezoglu O, Muchaneta-Kubara EC, *et al:* Myofibroblasts and the progression of diabetic nephropathy. *Nephrol Dial Transplant* 12:43–50, 1997
32. Valent P, Ashman LK, Hinterberg W, *et al:* Mast cell typing and demonstration of a distinct hematopoietic cell type and evidence of an immunophenotypic relationship to mononuclear phagocytes. *Blood* 73:1778–1785, 1989
33. Pang X, Sant G, Theoharides TC: Altered expression of bladder mast cell growth factor receptor (c-kit) in interstitial cystitis. *Urology* 51:939–944, 1998
34. Cepnis A, Konttinen YT, Takagi M, *et al:* Expression of Stem cell factor (SCF) and SCF receptor (C-kit) in synovial membrane in arthritis: Correlation with synovial mast cell hyperplasia and inflammation. *J Rheumatol* 25:2304–2314, 1998
35. Jernigan SM, Eddy AA: Experimental insights into the mechanisms of tubulo-interstitial scarring, in *Mechanisms and Clinical Management of Chronic Renal Failure*, edited by El Nahas AM, Oxford, Oxford University Press, 2000, pp 104–145