The role of macrophages in glomerulonephritis

David J. Nikolic-Paterson and Robert C. Atkins

Department of Nephrology and Monash University Department of Medicine, Monash Medical Centre,
Clayton, Australia

Abstract

Macrophage accumulation is a prominent feature in most types of human glomerulonephritis. In particular, tubulointerstitial macrophage accumulation correlates with the degree of renal dysfunction and is predictive of disease progression. Depletion studies have shown that macrophages can induce glomerular injury in experimental glomerulonephritis. Moreover, recent studies targeting chemokines and adhesion molecules have shown that inhibiting macrophage accumulation can suppress progressive renal injury in animal models of glomerulonephritis. Macrophages can produce many molecules with the potential to cause renal damage, although the precise mechanism(s) of macrophage-mediated renal injury have yet to be determined. It is now evident that tubules—a major source of chemokines and adhesion molecules—play an active role in promoting interstitial macrophage infiltration and activation. Thus, targeting pro-inflammatory functions of tubular epithelial cells may be an effective means to inhibit macrophage-mediated tubulointerstitial injury without causing systemic immunosuppression.

Keywords: adhesion molecules; cytokines; glomerulonephritis; macrophages; M-CSF; tubules

Macrophage accumulation in glomerulonephritis

Glomerular macrophage influx in the injured kidney was first demonstrated 25 years ago [1]. The culture of glomeruli isolated from patients with crescentic glomerulonephritis showed the presence of large numbers of highly motile cells. These were identified as macrophages on the basis of phagocytic function and ultrastructural characteristics [1]. Subsequent studies with monoclonal antibodies demonstrated that glomerular and interstitial macrophage infiltration occurs in most forms of primary and secondary glomerulonephritis [2,3]. Glomerular macrophage accumulation has been confirmed in many studies of human glomerulonephritis, but the relationship between macrophage numbers and the degree of renal dysfunction and proteinuria is controversial [4]. In contrast, there is a broad consensus that the number of interstitial macrophages correlates with the degree of renal dysfunction at the time of biopsy [4]. Indeed, the degree of interstitial macrophage accumulation predicts progression in lupus nephritis and IgA nephropathy [5,6]. This is consistent with the finding that tubulointerstitial rather than glomerular lesions correlate with renal dysfunction in human glomerulonephritis [7,8].

Glomerular and interstitial macrophage accumulation is also prominent in most experimental models of kidney disease, irrespective of whether the initial renal insult is mediated via immune or non-immune mechanisms [4]. Time-course studies have shown a close association between macrophage accumulation and the development of renal injury in many of animal disease models, including focal and segmental glomerulosclerosis and crescentic anti-GBM glomerulonephritis [9,10].

Experimental evidence that macrophages cause renal injury

Although studies in human glomerulonephritis strongly suggest a role for macrophages in causing renal injury, such descriptive data are not conclusive. This issue has been addressed by extrapolating the results of macrophage depletion in animal models of glomerulonephritis.

A number of different strategies have been used to block renal macrophage infiltration. Systemic irradiation with kidney shielding prevented glomerular macrophage infiltration and abolished proteinuria in rat accelerated anti-GBM disease [11]. Glomerular macrophage infiltration and proteinuria have also been blocked by administration of polyclonal anti-macrophage sera in models of anti-GBM disease, serum sickness and Heymann's nephritis [12–14]. A different approach is the use of a micro-encapsulated toxic drug, dichloromethylene diphosphonate, which is taken up preferentially by phagocytic cells. Although an efficient means to kill macrophages, such preparations can deplete circulating C3 levels. This method has been used to inhibit glomerular macrophage accumulation and proteinuria in anti-GBM glomerulonephritis [15], and to inhibit glomerular macrophage accumulation with a consequent reduction in mesangial matrix expansion in anti-Thy-1 mesangioproliferative nephritis [16].

Rather than systemic macrophage depletion, recent studies have focused on inhibiting the mechanisms by which blood monocytes are recruited into the kidney. Inhibiting the action of pro-inflammatory cytokines interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α) and macrophage migration inhibitory factor (MIF)—whose expression is markedly up-regulated in the injured kidney—has been shown to inhibit glomerular and interstitial macrophage infiltration and suppress renal injury in experimental glomerulonephritis [17–21]. The success of such cytokine blockade studies has been attributed to preventing up-regulation of chemokine and leukocyte adhesion molecule expression within the kidney. For example, IL-1 induces expression of monocyte chemotactic molecule-1 (MCP-1), macrophage colony-stimulating factor (M-CSF), intercellular adhesion molecule-1 (ICAM-1), osteopontin and CD44 by renal cell types [18,22–26]. Moreover, delaying cytokine blockade treatment until disease is already established has demonstrated a crucial role for cytokines such as IL-1 and MIF in progressive renal injury in rat crescentic anti-GBM glomerulonephritis [27,28].

Targeting of individual chemokines and adhesion molecules has also proven effective in inhibiting renal macrophage infiltration, thus both defining the molecules regulating blood monocyte recruitment and demonstrating the functional importance of macrophages in mediating renal injury. Blockade of chemokines (MCP-1, RANTES) or leukocyte adhesion molecules (ICAM-1, osteopontin) has been shown to inhibit macrophage accumulation and consequent renal injury in models of anti-GBM glomerulonephritis [29–33]. In addition, delaying chemokine or adhesion molecule blockade until disease is established is still effective in suppressing macrophage infiltration and renal injury [30,32,33]. Although these data are strongly supportive of a role for macrophages in causing renal injury in both the inductive and progressive phases of experimental kidney disease, it must be remembered that blockade of chemokines and adhesion molecules also suppresses T-cell infiltration and that renal injury in the commonly studied models (anti-GBM disease and lupus nephritis) is T-cell dependent.

Mechanisms of macrophage-mediated renal injury

Macrophages are important effector cells in both the adaptive and the innate immune response. In a similar fashion, it is thought that macrophages can mediate renal injury in both T-cell-dependent and -independent models of glomerulonephritis. Manoeuvers to block T-cell activation invariably suppress macrophage accumulation in parallel with inhibition of renal damage [34,35]. This is true whether such T-cell-targeted modalities are administered from the start of disease induction or delayed until disease is already established [34]. Thus, we can extrapolate that macrophages are the main effector population in T-cell-directed renal injury. In contrast, fewer studies have been performed in T-cell-independent models of glomerulonephritis. Irradiation-induced depletion was used to show that macrophages mediate the adverse effects of cholesterol feeding in rat puromycin aminonucleoside nephrosis (PAN) [36]. Similarly, irradiation-induced depletion has identified a role for macrophages promoting mesangial hypercellularity and mesangial matrix expansion in the rat remnant kidney [37]. Macrophage depletion in anti-Thy-1 mesangioproliferative nephritis also reduced mesangial matrix expansion, although proteinuria and mesangial cell proliferation were unaffected [16].

Macrophages are a heterogeneous population and can exhibit a wide array of responses depending upon the nature of the stimulus. In particular, macrophages can be stimulated to secrete a wide range of molecules which have the potential to cause renal damage. Macrophages and their products have been implicated in a number of pathological processes in glomerulonephritis, including: cell toxicity (reactive oxygen species, nitric oxide, TNF-α, complement factors); basement membrane damage (reactive oxygen species, metalloproteinases); decline in glomerular filtration rate (thromboxane A2); mesangial cell proliferation (PDGF, FGF-2, IL-1); crescent formation (IL-1, TNF-α, MIF, procoagulant activity); glomerulosclerosis; and interstitial fibrosis (TGF-β1, PDGF, FGF-2, fibronectin).

Specific inhibition of these individual mediators have shown that some of them (reactive oxygen species, IL-1, TNF-α, MIF, PDGF, TGF-β1, tissue factor) do indeed play pathogenic roles in experimental models of renal injury. However, these products are not unique to macrophages. Indeed, many of these products are also made by intrinsic renal cells in the diseased kidney. Thus, the relative contribution of macrophages to the renal injury caused by these mediators remains to be determined.

A new approach to understanding macrophage functions in the kidney is the use of adoptive transfer [38]. This involves perfusing macrophages (either a cell line or freshly prepared bone marrow-derived macrophages) into the renal artery such that some cells enter glomeruli and remain there for ∼24–48 h. For example, transfer of NR8383 macrophages into normal rats induced stromelysin production by resident glomerular cells [39]. This effect was dependent upon macrophage activation, since blockade of the transcription factor NF-κB in the transferred macrophages prevented the induction of stromelysin production [40]. In contrast, glomerular macrophage transfer into rats with anti-Thy-1 mesangioproliferative nephritis failed to induce stromelysin production by resident cells due to TGF-β production within the damaged glomerulus, indicating a potential beneficial effect of TGF-β in down-regulating macrophage-mediated renal injury [41,42]. This finding raises the issue of how the glomerular microenvironment affects macrophage function.

The concept macrophage 'programming' has been proposed by Rees and colleagues [43]. It is postulated that the glomerular microenvironment first encountered by a blood monocyte upon entry into the glomerulus determines the pattern, or programme, of responses that that cell can subsequently make. This is based upon experiments in which an initial cytokine exposure can render rat bone marrow-derived macrophages unresponsive to a different stimulus given several days later [44]. The relevance of these *in vitro* observations were shown in a study of acute rat anti-GBM glomerulonephritis in which macrophages isolated from inflamed, but not from normal glomeruli were shown to be unresponsive to the effects of anti-inflammatory cytokines in an assay of nitric oxide production [45].

A role for macrophages in renal repair

This review has focused on macrophages as a cause of renal injury. However, macrophage infiltration into the kidney may not always be detrimental since these cells have a number of functions that lend themselves to promoting renal repair. Macrophages are efficient at phagocytosing and removing apoptotic cells, deposited immune complexes and fibrin. In addition, macrophages can secrete hepatic growth factor and vascular endothelial growth factor, which can promote the repair of damaged tubules and endothelium, respectively.

Role of tubular cells in promoting interstitial macrophage accumulation

As discussed above, it is interstitial rather than glomerular macrophage accumulation that correlates with progressive loss of renal function in human glomerulonephritis. There is growing evidence that tubular epithelial cells may promote interstitial macrophage infiltration and activation [46]. *In situ* localization studies have shown that tubules are a major site of cytokine production (IL-1, TNF-α and MIF) in the injured kidney, cytokines being molecules that have a proven role in promoting interstitial macrophage infiltration and tubulointerstitial damage [21, 47–49]. In addition, tubules produce a number of chemokines (MCP-1, M-CSF, MIP-1β, MIP-2), and express various leukocyte adhesion molecules (osteopontin, ICAM-1, VCAM-1, CD44) [24,25,31,33,50,51]. Figure 1 illustrates the marked up-regulation of tubular M-CSF mRNA expression seen in rat anti-GBM glomerulonephritis. The increase in tubular M-CSF mRNA expression is closely related to local macrophage proliferation, macrophage accumulation and tubulointerstitial damage.

Experimental support for the postulate that tubules promote interstitial macrophage infiltration has come from studies using anti-sense oligonucleotides. This is based upon the fortuitous observation that oligonucleotides delivered systemically are, in part, taken up by proximal tubules, but not glomeruli, in a
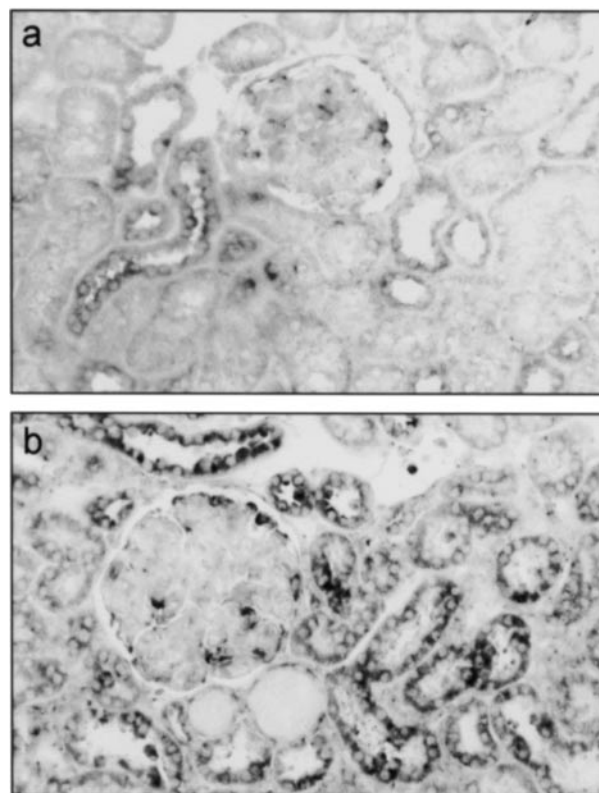

Fig. 1. (a) *In situ* hybridization showing constitutive macrophage colony-stimulating factor (M-CSF) mRNA expression in a few glomerular cells and ∼25% of cortical tubules in normal rat kidney. (b) Day 14 of rat anti-GBM glomerulonephritis shows a marked up-regulation of tubular M-CSF mRNA expression with most tubules positive. There is also an increase in glomerular M-CSF expression (mainly podocytes) and some interstitial M-CSF$^+$ cells are present. Original magnification ×200.

non-specific fashion. Using this strategy, Cheng *et al.* [52] showed that administration of an anti-sense ICAM-1 oligonucleotide reduced tubular ICAM-1 protein expression in mice with unilateral ureteric obstruction. The consequence was inhibition of interstitial macrophage accumulation and a remarkable preservation of tubulointerstitial architecture. This is interesting in the context of a study by Shappell *et al.* [53], who showed that histological damage and interstitial macrophage infiltration is unaffected following unilateral ureteric obstruction in lymphocyte-deficient (SCID) mice. Thus, it can be argued that macrophages cause tubulointerstitial injury independent of T-cells in this non-immune model of kidney damage.

A pivotal set of studies by Okada and colleagues [54,55] have demonstrated the potential for targeting tubular cell activation in progressive tubulointerstitial injury in glomerulonephritis. Using a model of anti-GBM glomerulonephritis induced in Wistar-Kyoto (WKY) rats, a period from day 27 to 37 was identified as the time at which significant interstitial macrophage infiltration and tubulointerstitial damage occurred. This was targeted by intravenous administration of anti-sense oligonucleotides for MCP-1 or osteopontin during this critical period. For each molecule targeted, anti-sense oligonucleotide treatment caused an ~ 50% reduction in interstitial macrophage accumulation, a reduction in tubulointerstitial damage and an improvement in renal function [54,55].

Conclusions

Based upon animal studies, it appears likely that the prominent macrophage infiltrates seen in biopsies of human glomerulonephritis mediate renal damage leading to a progressive loss of renal function. Substantial progress has been made in defining the chemotactic and adhesion molecules involved in regulating blood monocyte entry into the kidney. However, systemic chemokine or adhesion molecule blockade will inhibit blood monocyte recruitment at any site of inflammation and may thus not be desirable. There are two alternative strategies by which it may be possible to inhibit macrophage-mediated renal injury.

First, it is necessary to identify the precise mechanisms by which macrophages mediate renal injury. It may be possible to target such mechanisms through systemic drug delivery, such as the case for blocking cytokine (IL-1, TNF-α or MIF) function. However, if the mechanism cannot be safely targeted through systemic drug administration, e.g. it may not be desirable to systemically block TGF-β1, then macrophage-specific drug delivery systems (such as micro-encapsulation) could be employed. This approach depends upon the drug treatment leaving key host defense functions of the monocyte intact, such as entering sites of infection and killing invading micro-organisms through phagocytosis and nitric oxide production, while inhibiting those functions that mediate renal injury.

A second alternative strategy is to inhibit specifically the entry of blood monocytes into the tubulointerstitium without affecting monocyte recruitment into other sites of inflammation. This may be possible by targeting tubular production of chemokine and/or adhesion molecules using anti-sense oligonucleotides or via more generalized anti-inflammatory drugs using a vehicle delivery system with specificity for tubular epithelial cells.

References

1. Atkins RC, Holdsworth SR, Glasgow EF, Matthews FE. The macrophage in human rapidly progressive glomerulonephritis. *Lancet* 1976; 1: 830–832
2. Hooke DH, Hancock WW, Gee DC, Kraft N, Atkins RC. Monoclonal antibody analysis of glomerular hypercellularity in human glomerulonephritis. *Clin Nephrol* 1984; 22: 163–168
3. Hooke DH, Gee DC, Atkins RC. Leukocyte analysis using monoclonal antibodies in human glomerulonephritis. *Kidney Int* 1987; 31: 964–972
4. Nikolic-Paterson DJ, Lan HY, Atkins RC. Macrophages in immune renal injury. In: Neilson EG, Couser WG, eds. *Immunologic Renal Diseases*. Philadelphia, Lippincott-Raven, 1997: 575–592
5. Alexopoulos E, Seron D, Hartley RB, Cameron JS. Lupus nephritis: correlation of interstitial cells with glomerular function. *Kidney Int* 1990; 37: 100–109
6. Ootaka T, Saito T, Yusa A, Munakata T, Soma J, Abe K. Contribution of cellular infiltration to the progression of IgA nephropathy: a longtitudinal, immunocytochemical study on repeated biopsy specimens. *Nephrology* 1995; 1: 135–142
7. Risdon RA, Sloper JC, De Wardener HE. Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet* 1968; 2: 363–366
8. Bohle A, Christ H, Grund KE, Mackensen S. The role of the interstitium of the renal cortex in renal disease. *Contrib Nephrol* 1979; 16: 109–114
9. Saito T, Atkins RC. Contribution of mononuclear leucocytes to the progression of experimental focal glomerular sclerosis. *Kidney Int* 1990; 37: 1076–1083
10. Lan HY, Paterson DJ, Atkins RC. Initiation and evolution of interstitial leukocytic infiltration in experimental glomerulonephritis. *Kidney Int* 1991; 40: 425–433
11. Schreiner GF, Cotran RS, Pardo V, Unanue ER. A mononuclear cell component in experimental immunological glomerulonephritis. *J Exp Med* 1978; 147: 369–384
12. Holdsworth SR, Neale TJ, Wilson CB. Abrogation of macrophage-dependent injury in experimental glomerulonephritis in the rabbit. Use of an antimacrophage serum. *J Clin Invest* 1981; 68: 686–698
13. Matsumoto K. Production of interleukin-1 by glomerular macrophages in nephrotoxic serum nephritis. *Am J Nephrol* 1990; 10: 502–506
14. Hara M, Batsford SR, Mihatsch MJ, Bitter-Suermann D, Vogt A. Complement and monocytes are essential for provoking glomerular injury in passive Heymann nephritis in rats. Terminal complement components are not the sole mediators of proteinuria. *Lab Invest* 1991; 65: 168–179
15. Huang XR, Tipping PG, Apostolopoulos J *et al*. Mechanisms of T cell-induced glomerular injury in anti-glomeruler basement membrane (GBM) glomerulonephritis in rats. *Clin Exp Immunol* 1997; 109: 134–142

16. Westerhuis R, van SS, van DM *et al.* Distinctive roles of neutrophils and monocytes in anti-thy-1 nephritis. *Am J Pathol* 2000; 156: 303–310

17. Lan HY, Nikolic-Paterson DJ, Zarama M, Vannice JL, Atkins RC. Suppression of experimental crescentic glomerulonephritis by the interleukin-1 receptor antagonist. *Kidney Int* 1993; 43: 479–485

18. Tang WW, Feng L, Vannice JL, Wilson CB. Interleukin-1 receptor antagonist ameliorates experimental anti-glomerular basement membrane antibody-associated glomerulonephritis. *J Clin Invest* 1994; 93: 273–279

19. Hruby ZW, Shirota K, Jothy S, Lowry RP. Antiserum against tumor necrosis factor-alpha and a protease inhibitor reduce immune glomerular injury. *Kidney Int* 1991; 40: 43–51

20. Lan HY, Yang N, Metz C *et al.* TNF-alpha up-regulates renal MIF expression in rat crescentic glomerulonephritis. *Mol Med* 1997; 3: 136–144

21. Lan HY, Bacher M, Yang N *et al.* The pathogenic role of macrophage migration inhibitory factor in immunologically induced kidney disease in the rat. *J Exp Med* 1997; 185: 1455–1465

22. Rovin BH, Yoshiumura T, Tan L. Cytokine-induced production of monocyte chemoattractant protein-1 by cultured human mesangial cells. *J Immunol* 1992; 148: 2148–2153

23. Frank J, Engler-Blum G, Rodemann HP, Muller GA. Human renal tubular cells as a cytokine source: PDGF-B, GM-CSF and IL-6 mRNA expression in vitro. *Exp Nephrol* 1993; 1: 26–35

24. Nikolic-Paterson DJ, Lan HY, Hill PA, Vannice JL, Atkins RC. Suppression of experimental glomerulonephritis by the inter-leukin-1 receptor antagonist: inhibition of intercellular adhesion molecule-1 expression. *J Am Soc Nephrol* 1994; 4: 1695–1700

25. Yu XQ, Fan JM, Nikolic-Paterson DJ *et al.* IL-1 up-regulates osteopontin expression in experimental crescentic glomerulone-phritis in the rat. *Am J Pathol* 1999; 154: 833–841

26. Takazoe K, Foti R, Tesch GH *et al.* Up-regulation of the tumour-associated marker CD44V6 in experimental kidney disease. *Clin Exp Immunol* 2000; 121: 523–532

27. Lan HY, Nikolic-Paterson DJ, Mu W, Vannice JL, Atkins RC. Interleukin-1 receptor antagonist halts the progression of established crescentic glomerulonephritis in the rat. *Kidney Int* 1995; 47: 1303–1309

28. Yang N, Nikolic-Paterson DJ, Ng Y *et al.* Reversal of established rat crescentic glomerulonephritis by blockade of macrophage migration inhibitory factor (MIF): potential role of MIF in regulating glucocorticoid production. *Mol Med* 1998; 4: 413–424

29. Tang WW, Qi M, Warren JS. Monocyte chemoattractant protein 1 mediates glomerular macrophage infiltration in anti-GBM Ab GN. *Kidney Int* 1996; 50: 665–671

30. Lloyd CM, Minto AW, Dorf ME *et al.* RANTES and mono-cyte chemoattractant protein-1 (MCP-1) play an important role in the inflammatory phase of crescentic nephritis, but only MCP-1 is involved in crescent formation and interstitial fibrosis. *J Exp Med* 1997; 185: 1371–1380

31. Tesch GH, Schwarting A, Kinoshita K, Lan HY, Rollins BJ, Kelley VR. Monocyte chemoattractant protein-1 promotes macrophage-mediated tubular injury, but not glomerular injury, in nephrotoxic serum nephritis. *J Clin Invest* 1999; 103: 73–80

32. Nishikawa K, Guo YJ, Miyasaka m *et al.* Antibodies to inter-cellular adhesion molecule 1/lymphocyte function-associated antigen 1 prevent crescent formation in rat autoimmune glom-erulonephritis. *J Exp Med* 1993; 177: 667–677

33. Yu XQ, Nikolic-Paterson DJ, Mu W *et al.* A functional role for osteopontin in experimental crescentic glomerulonephritis in the rat. *Proc Assoc Am Physicians* 1998; 110: 50–64

34. Nishikawa K, Linsley PS, Collins AB, Stamenkovic I, McCluskey RT, Andres G. Effect of CTLA-4 chimeric protein

35. on rat autoimmune anti-glomerular basement membrane glomerulonephritis. *Eur J Immunol* 1994; 24: 1249–1254

35. Huang XR, Holdsworth SR, Tipping PG. Evidence for delayed-type hypersensitivity mechanisms in glomerular crescent forma-tion. *Kidney Int* 1994; 46: 69–78

36. Pesek-Diamond I, Ding G, Frye J, Diamond JR. Macrophages mediate adverse effects of cholesterol feeding in experimental nephrosis. *Am J Physiol* 1992; 263: F776–83

37. van Good H, van der Horst ML, Fidler V, Grond J. Glomerular macrophage modulation affects mesangial expansion in the rat after renal ablation. *Lab Invest* 1992; 66: 564–571

38. Kitamura M. Transfer of genetically engineered cells to the glomerulus. *Exp Nephrol* 1999; 7: 259–266

39. Kitamura M, Suto TS. Transfer of genetically engineered macrophages into the glomerulus. *Kidney Int* 1997; 51: 1274–1279

40. Kitamura M. Adoptive transfer of nuclear factor-κB-inactive macrophages to the glomerulus. *Kidney Int* 2000; 57: 709–716

41. Suto TS, Fine LG, Shimizu F, Kitamura M. *In vivo* transfer of engineered macrophages into the glomerulus: endogenous TGF-β-mediated defense against macrophage-induced glomerular cell activation. *J Immunol* 1997; 159: 2476–2483

42. Kitamura M. TGF-β1 as an endogenous defender against macrophage-triggered stromelysin gene expression in the glom-erulus. *J Immunol* 1998; 160: 5163–5168

43. Erwig LP, Rees AJ. Macrophage activation and programming and its role for macrophage function in glomerular inflamma-tion. *Kidney Blood Pressure Research* 1999; 22: 21–25

44. Erwig LP, Kluth DC, Walsh GM, Rees AJ. Initial cytokine exposure determines function of macrophages and renders them unresponsive to other cytokines. *J Immunol* 1998; 161: 1983–1988

45. Erwig LP, Stewart K, Rees AJ. Macrophages from inflamed but not normal glomeruli are unresponsive to anti-inflammatory cytokines. *Am J Pathol* 2000; 156: 295–301

46. Atkins RC, Nikolic-Paterson DJ, Lan HY. Tubulointerstitial injury in glomerulonephritis. *Nephrology* 1996; 2 [Suppl 1]: S2–S6

47. Tesch GH, Yang N, Yu H *et al.* Intrinsic renal cells are the major source of interleukin-1-β synthesis in normal and diseased rat kidney. *Nephrol Dial Transplant* 1997; 12: 1109–1115

48. Ma L, Yang B, Nikolic-Paterson DJ, Atkins RC, Wang H. Intercellular adhesion molecule-1 and tumour necrosis factor-α expression in human glomerulonephritis. *Nephrology* 1996; 3: 329–337

49. Lan HY, Yang N, Nikolic-Paterson DJ *et al.* Expression of macrophage migration inhibitory factor in human glomerulo-nephritis. *Kidney Int* 2000; 57: 499–509

50. Wuthrich RP. Vascular cell adhesion molecule-1 (VCAM-1) expression in murine lupus nephritis. *Kidney Int* 1992; 42: 903–914

51. Jun Z, Hill PA, Lan HY *et al.* CD44 and hyaluronan expression in the development of experimental crescentic glomerulo-nephritis. *Clin Exp Immunol* 1997; 108: 69–77

52. Cheng QL, Chen XM, Li F, Lin HL, Ye YZ, Fu B. Effects of ICAM-1 antisense oligonucleotide on the tubulointerstitium in mice with unilateral ureteral obstruction. *Kidney Int* 2000; 57: 183–190

53. Shappell SB, Gurpinar T, Lechago J, Suki WN, Truong LD. Chronic obstructive uropathy in severe combined immuno-deficient (SCID) mice: lymphocyte infiltration is not required for progressive tubulointerstitial injury. *J Am Soc Nephrol* 1998; 9: 1008–1017

54. Okada H, Moriwaki K, Kalluri R *et al.* Inhibition of monocyte chemoattractant protein-1 expression in tubular epithelium attenuates tubulointerstitial alteration in rat Goodpasture syndrome. *Kidney Int* 2000; 57: 927–936

55. Okada H, Moriwaki K, Kalluri R *et al.* Osteopontin expressed by renal tubular epithelium mediates interstitial monocyte infiltration in rats. *Am J Physiol* 2000; 278: F110–F121