Inflammatory Cells in Renal Injury and Repair

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Summary: Renal inflammation may result from a myriad of insults and often is characterized by the presence of infiltrating inflammatory leukocytes within the glomerulus or tubulointerstitium. Accumulating evidence indicates that infiltrating leukocytes are key players in the induction of renal injury. Although renal inflammation often is followed by the development of fibrosis with loss of renal function, it can resolve. Resolution may be spontaneous as in poststreptococcal glomerulonephritis or after the administration of effective treatment such as immunosuppressive agents. The mechanisms and cells underlying the resolution process and the exact temporal sequence remains uncertain at present but likely involves the removal of injurious leukocytes, the down-regulation of immune responses, and the alteration of the phenotype of infiltrating macrophages from proinflammatory to prorepair. In this review we examine the role of leukocytes in both renal inflammation and repair.
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Renal inflammation is a feature of various forms of glomerular and tubulointerstitial injury. Severe acute or persistent chronic disease may lead to glomerulosclerosis, renal tubular atrophy, loss of the nourishing microvascular network, and interstitial scarring with an accompanying loss of renal function. Thus, strategies that prevent or inhibit renal inflammation would be of great potential therapeutic benefit. An additional future challenge is to understand the mechanisms involved in renal repair and to use them to devise novel therapies to promote renal healing including the reversal of scarring and the restoration of normal tissue architecture. In this review we discuss the role of leukocytes in both renal inflammation and repair, although there are little data regarding the latter.

It is important to note at the outset that severe renal inflammation may resolve completely (Fig. 1). For example, poststreptococcal glomerulonephritis (GN) may develop after a skin or throat infection and typically shows the histologic appearance of diffuse proliferative GN with prominent infiltration by macrophages (Mϕ) and neutrophils (PMN). Despite the severity of the histologic lesion, poststreptococcal GN typically resolves over 1 to 2 weeks with complete restoration of normal glomerular structure and function and this highlights the natural endogenous repair mechanisms that exist to promote renal repair. There also have been reports of patients with conditions such as lupus nephritis with improved rather than stabilized renal function after treatment, suggesting a partial resolution of the underlying disease process. Furthermore, some of the features of diabetic nephropathy may regress after pancreas transplantation whereas severe forms of acute GN such as antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis associated with crescent formation may resolve with specific anti-inflammatory immunosuppressive treatment.

Experimental animal models of renal disease show similar variations in outcome. Nephrotoxic nephritis (NTN) induced by the adminis-

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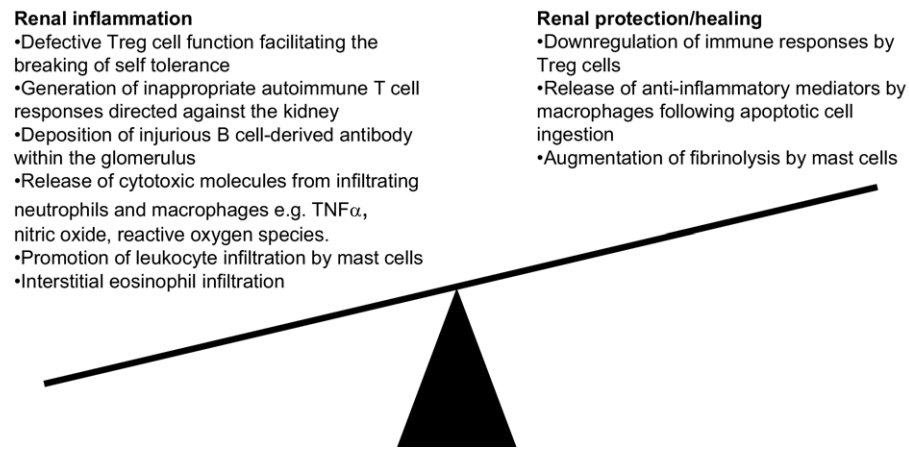

Figure 1. The balance between continued inflammation and healing. Renal inflammation may be chronic and progress to fibrotic scarring and end-stage renal failure, but complete or partial resolution can occur. Many leukocytes collaborate in the initiation and progression of inflammation and may be involved in many other injurious processes other than those depicted. Also, the factors that dictate whether resolution may occur will vary according to nature of the disease process.

tration of heterologous antibody directed at glomerular components or unilateral ureteric obstruction (UUO) has aided the study of inflammatory cells in renal inflammation and progressive scarring. In contrast, the resolving rat model of Thy 1.1 model of GN, which has some features of human mesangioproliferative GN, has provided insight into the beneficial role of apoptosis in tissue remodeling.

CELLULAR MEDIATORS OF RENAL INFLAMMATION

The pathogenesis of renal inflammation is complex and multifaceted involving the interplay of chemokines, adhesion molecules, and cytokines. However, irrespective of the initial insult, renal inflammation is characterized by glomerular and tubulointerstitial infiltration by inflammatory cells including neutrophils, macrophages, and lymphocytes. Such cellular infiltrates are evident in experimental models of renal disease and human renal biopsy specimens.

PMNs

PMN influx often is present in acute renal injury such as ANCA-positive vasculitis, poststreptococcal glomerulonephritis, and ischemia-reperfusion injury. Although PMNs are less evident in the later stages of many diseases, PMN production of reactive oxygen species and proteases in acute injury is an important component of renal inflammation.[1] Recent work has shed light on the role of both proteinase 3 and myeloperoxidase ANCA in small-vessel vasculitis. ANCA can activate PMNs by binding to both cell surface–expressed proteinase 3, myeloperoxidase, and Fc-gamma receptors and this induces protease release, superoxide generation, and cytokine release that may directly injure endothelial cells and fuel the inflammatory response.[2] ANCA antibodies also may activate monocytes in a similar mechanism. ANCA also reduces the ability of PMNs to deform—a prerequisite for the successful passage through capillary beds—and this may result in the sequestration of activated PMNs in capillaries, where they may induce tissue injury.[3]

LYMPHOCYTES AND DENDRITIC CELLS

T cells, B cells, and dendritic cells are key components of the adaptive immune system and play important roles in renal inflammation driven by aberrant immunologic responses. Although T cells may be directly cytotoxic, they also facilitate the activation of other cells including macrophages via interferon-γ production and B lymphocytes, leading to antibody production. Naive CD4+ T cells may adopt different phenotypes according to the cytokine

environment with interleukin (IL)-12/IL-18 promoting a Th1 phenotype and IL-4/IL-13 promoting a Th2 phenotype. Th1 cells promote delayed-type hypersensitivity reactions and the generation of complement-fixing antibodies whereas Th2 cells promote allergic responses and the generation of immunoglobulin E and antibodies with a lesser capacity to fix complement. Experimental data indicate that severe crescentic glomerulonephritis is driven by a Th1 immune response whereas the Th2 immune response favors antibody production and the formation of glomerular immune deposits (reviewed in Tipping and Holdsworth[4]). Indeed, the administration or blockade of the cytokines that influence the development of Th1 or Th2 responses can exacerbate (eg, IL-12 administration or IL-4 deficiency) or ameliorate disease (eg, IL-4 administration or IL-12 deficiency), reinforcing the role of T cells and their immunologic phenotype in renal inflammation.

CD8+ cells can be found in experimental and human GN and have been shown to contribute to the development and progression of NTN in the Wistar Kyoto (WKY) rat.[5] In contrast, CD8 deficiency does not affect the course of NTN in mice.[6]

Interestingly, an accumulating body of evidence has implicated lymphocytes in the pathogenesis of ischemia-reperfusion injury—a process previously associated primarily with neutrophils[7]—although the picture is complicated. T-cell– and B-cell–deficient mice are significantly protected from renal ischemia-reperfusion injury with adoptive transfer experiments, suggesting an important role for CD4+ T cells and serum factors generated by B cells.[8,9] Despite these findings, the combined deficiency of T and B cells found in recombinase activating gene-1–deficient mice was not protective.[10] Furthermore, the adoptive transfer of either T or B cells into recombinase activating gene-1–deficient mice was protective, highlighting the complexity of the cellular interactions in this model.

Dendritic cells play an important role in the maintenance of tolerance as well as mounting robust immune responses to pathogens, and so forth. They are highly efficient antigen presentation cells and present antigen to T cells in the context of various costimulatory molecules. Although the cellular interaction at the immunologic synapse may be disrupted, the results of such interventions can be variable. For example, although CD80 and CD86 on the dendritic cell surface interact with CD25 borne by the T cell, deficiency of either or both molecules has a completely different effect in anti-glomerular basement membrane (GBM) glomerulonephritis: CD80 deficiency is protective, CD86 deficiency exacerbates disease, whereas combined CD80/CD86 blockade has no effect.[11]

Regulatory T Cells

Immune responses must be tightly regulated or the immune system would be overwhelmed. Regulatory T cells (Treg) are a subset of T cells that play an important role in the maintenance of peripheral tolerance with defective Treg function being involved in the pathogenesis of autoimmunity including glomerulonephritis.[12,13] They are characterized by the markers CD25 and FoxP3 and may produce immunosuppressive cytokines such as IL-10 and transforming growth factor-β. The key role of Treg cells in suppressing autoimmune disease was shown in a recent study of lupus-prone New Zealand Mixed 2328 mice.[13] Thymectomy performed on the third day of life markedly accelerated the development of widespread autoimmune disease affecting multiple organs. This was suppressed effectively by the adoptive transfer of CD25+ T cells from asymptomatic mice, thereby suggesting that the development of disease in these lupus-prone mice resulted from a deficiency of Treg cells. It also has been shown that Treg cells may modulate experimentally induced and spontaneous renal inflammation. The adoptive transfer of 1,000,000 CD4+ CD25+ Treg cells derived from mice immunized with rabbit immunoglobulin to mice that subsequently received nephrotoxic rabbit anti-GBM serum resulted in marked protection from disease compared with control mice that received CD4+ CD25- cells.[14] The kidneys of the mice that received the CD4+ CD25+ Treg cells showed reduced infiltration with T cells (CD4 and CD8) and macrophages, as well as reduced expression of proinflammatory cytokines. In addition, tracking experiments revealed that the administered Treg cells did not localize to the

kidneys but were found in the secondary lymphoid organs.

There also is evidence suggesting that Treg cells may protect patients from future autoimmune disease. For example, the majority of patients recovering from Goodpasture's (anti-GBM) disease develop a population of CD25+ T cells from 3 months onward that are capable of suppressing T-cell responses to the Goodpasture antigen in vitro.[15] Although the immunosuppressive mechanism used by these CD25+ Treg cells was not elucidated, this study suggested that the development of such a Treg population may explain why Goodpasture's disease is typically a one-shot illness.

Treg cells also are likely to be key players in the regulation of the immune response to renal allografts. The development of donor-specific Treg cells was responsible for the protective effect of a pretransplant donor peripheral mononuclear cell infusion in a rat renal transplant model.[16] Human transplant recipients may develop Treg cells that limit immune responses to mismatched human leukocyte antigen DR antigens,[17] although Treg cells do not appear to be involved in limiting direct pathway hyporesponsiveness in stable allograft patients.[2] It also is pertinent that the numbers of Treg cells is affected differentially by immunosuppressive agents, with patients receiving calcineurin inhibitors showing a reduced percentage of CD4+ CD25+ Fox P3+ Treg cells compared with patients receiving rapamycin.[18] Methods are now being developed to expand the small numbers of Treg cells present in peripheral blood to facilitate greater functional analysis.[17] Thus, it may be possible to monitor Treg cell numbers and function in transplant recipients and patients with glomerulonephritis in the future and titrate immunosuppressive treatment accordingly.

As a result of their capacity to down-regulate injurious immune responses directed at the kidney and to restore immunologic calm, the administration or manipulation of Treg cells undoubtedly holds great therapeutic promise.[19,20] Interestingly, it may be the case that therapeutic interventions not directly aimed at Treg cells may, at least in part, exert their effects via the modulation of Treg cells. For example, anti-CD20 antibody (rituximab) was administered to 22 patients with lupus nephritis in a recent pilot study.[21] CD20 is expressed exclusively on human B cells and rituximab treatment depletes circulating B cells for 6 to 9 months. Treatment resulted in B-cell depletion, a reduction in proteinuria, but no effect on autoantibody levels over 3 months. Intriguingly, however, a sustained increase in the level and immunosuppressive efficacy of Treg cells was noted, suggesting that rituximab therapy may modulate Treg cells beneficially.

B Cells

B cells are key players in the humoral component of acute renal inflammation whether it is in the setting of acute GN or humoral rejection of a renal transplant. As indicated previously, B-cell–deficient mice are protected from renal ischemia-reperfusion injury and this appears to be the result of a serum factor rather than B cells.[9] As indicated previously, treatment with rituximab shows early promise in lupus nephritis and can induce disease remission in ANCA-positive vasculitis—a disease characterized by the presence of the pathogenic ANCA autoantibody.[22] In addition, idiopathic membranous nephropathy is characterized by both immunoglobulin G deposition, generated in response to an as yet unknown antigen, and a focal or diffuse CD20+ B-cell infiltrate.[23] Early work suggests that rituximab may be a promising treatment for the treatment of membranous nephropathy.[24] The exact mechanisms underlying these effects on acute and chronic renal inflammation still require elucidation because, although reduced autoantibody production is a logical mechanism, disease may remit without a change in autoantibody levels. Thus, B cells are very likely to have other important roles in these diseases including antigen presentation and modulation of Treg cell numbers and functions.

EOSINOPHILS AND MAST CELLS

Eosinophils are associated classically with allergic responses and parasitic infections and contain various proinflammatory factors such as eosinophil cationic protein, which can induce

tissue injury. Eosinophils are key effector cells in the Churg-Strauss syndrome and patients with renal involvement may develop renal eosinophilic infiltration with eosinophiluria.[25] A prominent eosinophil infiltrate often is evident in drug-related acute interstitial nephritis despite the fact that T cells also are implicated in this condition.[26] Eosinophils also may infiltrate the kidney during allograft rejection,[27] although drug-related interstitial nephritis also should be considered whenever eosinophils are present.[28] Also, the serum levels of IL-5 (a key mitogen and survival factor for eosinophils) and eosinophil cationic protein were higher in pediatric patients with Henoch Schonlein purpura complicated with renal involvement compared with those patients without nephritis.[29] Unlike other circulating leukocytes, the basophil does not contribute significantly to renal inflammation.

Mast cell are tissue cells of hematopoietic origin and are able to secrete a variety of mediators such as histamine, cytokines, chemokines, and so forth. Recent work suggests that mast cells contribute to renal disease with tubulointerstitial mast cell infiltration evident in various human diseases such as lupus nephritis, focal segmental glomerulosclerosis, ANCA-associated GN, as well as diabetes, in which mast cell numbers correlated with interstitial fibrosis.[30] Increased mast cell numbers also have been noted in chronic renal ischemia[31] and transplant rejection.[32] Intriguingly, recent experimental work suggests a beneficial effect of mast cells because mast cell–deficient mice showed an increased mortality and worse histopathologic disease in a rabbit anti-GBM model of GN.[33] Mast cell–deficient mice showed more severe subendothelial deposits consisting of fibrin and collagen, suggesting that mast cells play an active role in the fibrinolysis system. In contrast, mast cell–deficient mice were protected from injury in sheep anti-GBM GN and showed reduced expression of adhesion molecules, infiltrating T cells, and macrophages.[34] In addition, mast cell–derived factors modulate dendritic cell function at a site of immunization and suppress antigen-specific Th1 responses, indicating their capacity to affect immune response.[34] The role of mast cells in both renal inflammation and repair undoubtedly merits further study.

Mϕ

Mϕ are key inflammatory cells and are strongly implicated in renal injury (Fig. 2). A recent study using conditional Mϕ ablation in the carbon tetrachloride model of hepatic inflammation and scarring indicated differential roles of Mϕ in different phases of the model. Mϕ depletion during the injury phase of the model was protective whereas Mϕ depletion during the resolving phase resulted in defective tissue remodeling and persistence of fibrotic tissue.[35] This key study confirmed that Mϕ can play a key role in tissue remodeling but comparable studies in the kidney are currently lacking.

Mϕ and Apoptosis

Mϕ are capable of generating numerous cytotoxic mediators and may induce apoptosis in both mesangial cells and tubular epithelial cells in vitro.[36,37] Coculture experiments with mesangial cells have indicated the critical involvement of Mϕ-derived nitric oxide (NO), a lesser role for tumor necrosis factor-α, and no demonstrable involvement of Fas ligand.[36] Mϕ-derived NO also inhibits mesangial cell proliferation and NO-mediated inhibition of mesangial proliferation, and induction of apoptosis could be the ideal weapon to combat mesangial proliferative nephritis. Although monocyte/Mϕ depletion has been performed in the Thy1.1 model and does reduce extracellular matrix deposition, the effects on the mesangial cell numbers during the resolution phase were not studied.

Mϕ and Glomerulonephritis

The important role of Mϕ has been shown in a variety of experimental models such as NTN in the rat.[38] The induction of a leukopenia with cyclophosphamide is protective in rat NTN, with injury being restored by intravenous administration of a Mϕ cell line as a means of reconstitution.[39] We used a murine conditional Mϕ ablation model to deplete Mϕ in progressive crescentic NTN. The depletion of Mϕ between days 15 and 20 reduced glomerular crescent formation, tubular cell apoptosis, in-

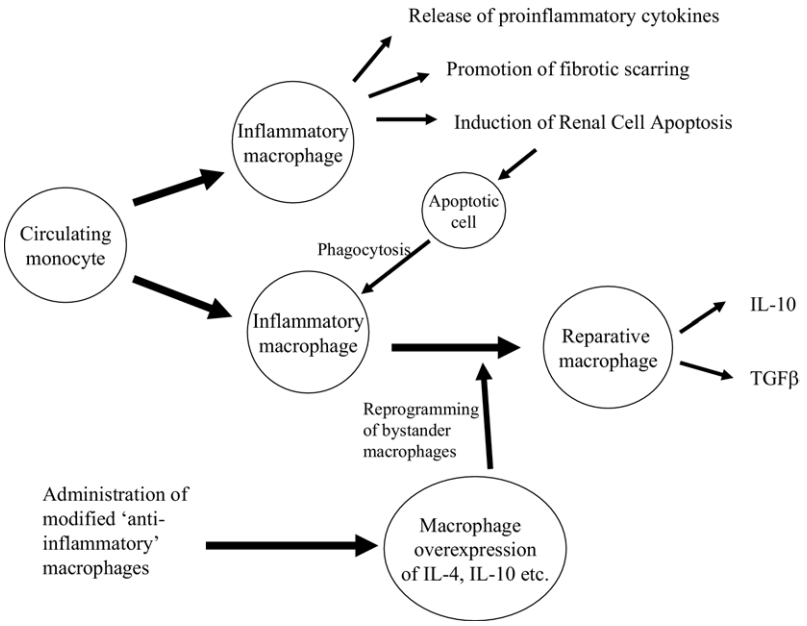

Figure 2. Macrophages in renal disease. Macrophages are key players in renal inflammation but are multifunctional cells that may induce tissue injury or promote repair. Inflammatory macrophages may release myriad proinflammatory mediators, induce renal cell apoptosis, and promote fibrotic scarring. Macrophages, however, may be reprogrammed by the ingestion of apoptotic cells or exposure to anti-inflammatory cytokines and then may act to dampen down inflammatory processes by the secretion of IL-10, transforming growth factor β, and so forth. The administration of modified macrophages can ameliorate injury and this may be caused, at least in part, by the reprogramming of bystander macrophages.

terstitial fibrosis, proteinuria, and improved renal function, thereby reinforcing a major injurious role for infiltrating Mϕ.[40]

Mϕ and Tubulointerstitial Disease

The UUO model has proved valuable for the study of the pathogenesis of inflammation and scarring within the tubulointerstitium. Previous work has shown that the UUO model is lymphocyte independent whereas PMN infiltration is not evident. Classically activated Mϕ are eminently capable of inducing apoptosis in renal tubular epithelial cells.[37,41,42] Several investigators have noted that mice with a diminished interstitial Mϕ infiltrate in UUO showed a reduced level of tubular cell apoptosis.[43,44] Furthermore, pharmacologic inhibition of the production of inducible nitric oxide synthase (iNOS)-derived NO, an effective inducer of tubular cell death in vitro, also protected tubular cells in vivo without affecting interstitial Mϕ numbers.[37]

Renal ischemia-reperfusion injury plays a key role in the development of acute renal failure in many patients and, until recently, PMNs were regarded as the inflammatory cells that were involved in much of the tissue injury associated with renal ischemia-reperfusion injury. Recent work, however, has suggested that Mϕ may be implicated. Mϕ depletion using liposomal clodronate in a rat model of renal ischemia-reperfusion injury attenuated the degree of tubular necrosis and apoptosis and diminished proinflammatory cytokine expression at the messenger RNA level.[45] In addition, mice deficient for C-C chemokine receptor 2 (CCR2) (the ligand for monocyte chemoattractant-1 [MCP-1]) were protected from renal ischemia-reperfusion injury and showed reduced acute tubular necrosis, preserved renal function, reduced Mϕ infiltration, and a diminished number of iNOS-positive interstitial cells.[46] Interestingly, the injured kidneys of the CCR2-deficient mice also showed reduced expression of PMN chemokines (keratinocyte chemoattractant chemokine [KC] and macrophage inflammatory protein-2 [MIP-2]) and a reduced PMN infil-

trate, suggesting that monocyte/Mϕ may partly regulate PMN infiltration in renal inflammation.

Mϕ and Transplantation

Despite advances in immunosuppression, acute and chronic rejection of renal and other solid organ transplants still is problematic. Although the lymphocytes of the adaptive immune system are believed to be the generals orchestrating the immunologic rejection of allografts, it may be the case that Mϕ are important foot soldiers. Mϕ are evident in human biopsy specimens of renal allografts with acute or chronic rejection and are the predominant leukocyte in arteritis in human rejection.[47] Also, the Mϕ index correlates with the long-term outcome of allografts.[48]

Key experimental studies used clodronate-mediated depletion of Mϕ in a rat model of acute transplant rejection, resulting in approximately 75% of intragraft macrophages being depleted or undergoing apoptosis. Mϕ depletion resulted in marked protection of the allograft with diminished histologic damage, improved renal function,[49] and reduced expression of IL-18,[50] whereas infiltration by other leukocyte populations was unaffected. Interestingly, the expression of iNOS was reduced dramatically, again suggesting that iNOS-derived NO is a key effector of tissue damage in these rodent models. Mϕ may proliferate within inflamed kidneys and intrarenal Mϕ proliferation does contribute to the accumulation of Mϕ within the graft because the administration of function-blocking antibody to Mϕ colony-stimulating factor reduced Mϕ numbers in a murine model of acute renal allograft rejection and protected the graft from injury.[51]

Mϕ and Diabetes

Diabetic nephropathy has long been regarded as a metabolic disease but there is an accumulating body of evidence that implicates the Mϕ in the development of diabetic nephropathy. Infiltrating Mϕ are found in kidneys of patients with diabetic nephropathy.[52-54] Data from rodent models show that this is stimulated by hyperglycemia, and predates many of the other histologic changes.[54,55] In addition, MCP-1–deficient mice show partial protection from experimental diabetic renal disease[56] induced by the administration of streptozotocin, with a reduction in the number of interstitial iNOS-positive Mϕ being noted.[57]

Treatment with Modified Mϕ

Mϕ ideally are suited to alter inflammatory disease because of their preferential localization to inflamed tissue and their suitability for ex vivo manipulation involving genetic, cytokine, or chemical manipulation. Thus, monocyte/Mϕ have been used as a Trojan horse to infiltrate inflamed sites and release anti-inflammatory mediators that diminish tissue injury and facilitate tissue repair. The administration of Mϕ overexpressing IL-10, IL-4, or IL-1–receptor antagonist or a dominant-negative inhibitor of the nuclear factor κ B pathway were able to ameliorate glomerular and interstitial inflammation in various rodent models.[57-60] An interesting feature of this approach is that the localization of the modified Mϕ appears to be able to beneficially alter the phenotype of bystander infiltrating Mϕ and resident renal cells[57,58] such that the administration of a small number of Mϕ with altered function is able to produce a sustained re-orientation of the inflammatory response.

RESOLUTION OF RENAL INFLAMMATION

There are several requirements for the resolution of renal injury to occur including the removal of the initiating insult, reversion of renal cells to their normal quiescent phenotype, and a change in the cytokine milieu from proinflammatory to prorepair. From the leukocyte perspective, the key processes are the removal of infiltrating leukocytes and reprogramming of infiltrating proinflammatory macrophages to a reparative phenotype. There are limited possibilities for leukocyte removal because they may die by undergoing apoptosis within the kidney or emigrate via lymphatic vessels.

PMNs constitutively undergo apoptosis in experimental and human disease and are ingested readily by Mϕ at inflamed sites. Study of radiolabeled PMNs in a rat model of immune complex GN indicated that, although approximately 20% of infiltrating glomerular PMNs underwent

apoptosis and were cleared by phagocytosis, the majority of PMNs left the kidney before undergoing apoptosis and were cleared elsewhere in the reticuloendothelial system. The proportion of PMNs that die in situ within the kidney, however, is likely to vary according to the nature of the disease process.

The removal of Mϕ and lymphocytes from the inflamed kidney has been little studied. Limited available data suggest that infiltrating Mϕ either may undergo apoptosis within the inflamed kidney or exit to draining lymph nodes, which is different from the fate of Mϕ in nonrenal inflammation such as experimental peritonitis, in which inflammatory Mϕ do not die at the inflamed site but traffic to draining lymph nodes. Mϕ trafficking during and after glomerular inflammation merits further study. Similarly, little is known regarding the fate of infiltrating lymphocytes, although it would be logical to assume that they traffic to draining lymph nodes.

The ingestion of apoptotic cells such as PMNs by Mϕ is a powerful biological stimulus and reprograms the Mϕ to an anti-inflammatory phenotype.[61] The administration of apoptotic cells to inflamed sites has been shown to promote the resolution of inflammation and it therefore also is likely to be important in the resolution of GN. It is of interest that glucocorticoids increase the capacity of Mϕ to ingest apoptotic cells, although it is unclear whether this action is important in their beneficial action on inflammatory GN. It also is pertinent that the defective phagocytosis of apoptotic cells as is found in C1q-deficient mice can lead to the development of spontaneous autoimmune GN and more severe glomerular injury in experimental NTN.[62] It obviously is pertinent that most human patients with C1q deficiency develop SLE whereas Mϕ from patients with systemic lupus erythematosis (SLE) show decreased capacity to phagocytose apoptotic cells.[63] Such defective apoptotic cell clearance may result in inadequate deactivation of infiltrating inflammatory Mϕ and promote ongoing tissue injury. Also, defective or inadequate apoptotic cell uptake may place mesangial cells at risk of ongoing Mϕ cytotoxicity because in vitro data has indicated that uptake of apoptotic cells diminishes Mϕ induction of mesangial cell apoptosis by tumor necrosis factor-α.[64] However, the effect of such phagocytic defects on the resolution of glomerular injury has not been studied.

CONCLUSIONS AND FUTURE PROSPECTS

Although the role of key cytokines such as tumor necrosis factor-α and interleukin-1 are described elsewhere, it is important to note that the beneficial effects of cytokine blockade in experimental models and in human disease are likely to be mediated, at least in part, by inhibitory effects on leukocyte infiltration and activation. Our current therapies for inflammatory GN focus on reducing the proinflammatory behavior of leukocytes, inhibiting cell division, or targeting proinflammatory mediators such as tumor necrosis factor-α. The role of leukocytes in the resolution of glomerular inflammation and associated glomerular remodeling still are incompletely understood. However, future work will provide insights that should lead to novel therapies that harness the reparative power of leukocytes in renal disease.

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