Trends in Molecular Medicine

CellPress

Review

The Changing Landscape of Renal Inflammation

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Kidney inflammation is a major contributor to progressive renal injury, leading to glomerulonephritis (GN) and chronic kidney disease. We review recent advances in our understanding of leukocyte accumulation in the kidney, emphasizing key chemokines involved in GN. We discuss features of renal inflammation such as the evolving concept of immune cell plasticity. We also describe certain aspects of organ-specific tissue microenvironments in shaping immune cell responses, as well as the current knowledge of how regulatory T lymphocytes impact on other immune effector cell populations to control inflammation. It is clear that present and future research in these areas may contribute to the development of novel targeted therapeutics, with the hope of alleviating the burden of end-stage renal disease (ESRD).

Kidney Inflammation and ESRD

The prevalence of ESRD is increasing worldwide and is associated with high mortality and morbidity. **Glomerulonephritis** (GN) (see Glossary), either in the context of a systemic condition (autoimmune disease, infections) or as a primary disease, is the third cause of ESRD in the USA and accounts for nearly 10% of cases [1], a figure that is probably much higher in developing countries. In addition, in **diabetic** and **hypertensive nephropathy**, the two primary causes of ESRD, as well as in renal ischemia–reperfusion injury, kidney inflammation contributes to progressive kidney damage that eventually leads to loss of glomeruli, tubular atrophy and fibrosis, with a concomitant decrease in glomerular filtration rate. Therefore, an understanding of the molecular pathways driving persistent renal inflammation is essential to decipher the pathogenesis of various forms of kidney diseases and to develop novel and more-efficient targeted therapeutics to prevent ESRD.

Kidney inflammation can be induced by a variety of triggers including infection, ischemia–reperfusion, *in situ* immune-complex formation or deposition, as well as by complement pathway dysregulation. Inflammation encompasses leukocyte recruitment, systemic and local regulation of leukocyte reactions, and termination of these processes. The appropriate balance of these inflammatory responses allows defense against invading pathogens and/or tumor cells while limiting collateral damage. By contrast, the dysregulation of any of these responses sets the stage for inflammatory disease, as in the case of chronic GN.

In this article we detail some recent advances in our understanding of mechanisms regulating leukocyte accumulation during renal inflammation, some which have been made possible using multiphoton intravital microscopy (IVM). We discuss new insights into the interactions of regulatory immune cells with effectors cells in the control of renal inflammation. Lastly, we conclude with a perspective on potential therapeutic targets that may recalibrate regulatory nodes and thus limit inflammation-induced kidney damage.

Trends

Leukocyte recruitment in the specialized microvasculature of the renal glomerulus differs from the classical paradigm of leukocyte rolling, arrest, and transmigration.

The local inflammatory microenvironment is largely defined by the local production of chemokines, which orchestrate leukocyte accumulation and can contribute to kidney dysfunction, as is the case in GN.

Factors such as sodium levels, uremia, or changes in the microbiota may reset homeostatic equilibria in the kidney, thus influencing the immune response.

Expanding subsets of immune regulatory cells help to maintain immune homeostasis. Regulatory T cells are particularly important in limiting inflammatory kidney damage.

The concept of T cell plasticity has questioned some aspects of lineage commitment and terminal differentiation of leukocyte subsets.

One of the challenges of targeted renal immunotherapy is attempting to balance and specifically elicit suppressive regulatory responses while inhibiting potentially damaging effector cell functions in the local kidney microenvironment.

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Leukocyte Accumulation in the Kidney: Patrolling and Adhesion

Leukocyte Recruitment in the Specialized Microvasculature of the Kidney

Leukocyte recruitment is the hallmark of inflammation. Local production of chemokines orchestrates their migration from the peripheral blood circulation into inflamed tissue via a well-described complex cascade of events. These include leukocyte capture, rolling, slow rolling, arrest, adhesion, crawling, and eventual transmigration. The advent of advanced IVM has permitted a better description and analysis of leukocyte recruitment *in vivo*, unveiling the complexity of leukocyte accumulation in the specialized microvasculature of the kidney [2]. Recent studies are beginning to uncover unique pathways of leukocyte accumulation in glomeruli, which may vary in response to different stimuli (Figure 1, Key Figure). Monocytes patrol the vascular endothelium removing damaged cells and debris, and thus help to limit inflammation and maintain immune homeostasis [3]. Neutrophils also appear to be active in immunosurveillance because they have been observed to crawl within the glomeruli of untreated animals [4]. However, a caveat is that IVM requires the surgical exteriorization of the kidney in live animals, so the prevalence of leukocyte immunosurveillance in an unmanipulated kidney remains to be determined. Upon induction of acute, anti-GBM (glomerular basement membrane) antibody-mediated nephritis in mice, leukocytes do not roll on the vessel wall via selectins but simply arrest. Neutrophils increase their dwell time within glomerular capillaries, and generate reactive oxygen species, but do not transmigrate, at least in this acute setting [4]. The mechanisms of glomerular leukocyte accumulation in a more chronic setting and the steps involved in T cell accumulation have not been investigated. Moreover, the mechanisms allowing T cells to detect cognate antigen in a setting where leukocytes appear to remain primarily intravascular remain to be elucidated.

The pathways of leukocyte accumulation in the kidney will likely depend on the primary site of damage (glomerulus versus tubulointerstitium) and the instigating stimulus. For example, unlike the glomerulus, selectin-mediated rolling followed by arrest of leukocytes is observed in small vessels of the tubulointerstitium following tissue damage induced by kidney ischemia–reperfusion [5] or kidney graft rejection [6]. Although not yet directly evaluated in the kidney by IVM, the stimulus will dictate the molecular requirements for leukocyte accumulation. For example, in the liver, neutrophil sequestration in mouse liver sinusoids in response to lipopolysaccharide (LPS) appears to rely on CD44 and hyaluronan [7], representing an unusual pathway that is distinct from the classical ligand–receptor interactions of integrins. However, in response to sterile injury (Nlrp3 inflammasome), neutrophil accumulation is mediated by the classical leukocyte adhesion molecule Mac-1 [8]. In the kidney, in the context of glomerular IgG deposition, Fcγ-receptors on leukocytes may play a key role in recruitment because they may tether to the Fc portion of deposited IgG accessible to circulating blood through open endothelial fenestrae [9]. Direct evidence for this mechanism using multiphoton IVM is currently lacking. However, the induction of glomerular neutrophil accumulation following acute, anti-GBM nephritis in mice that only express FcγRs selectively on neutrophils suggests that this might be the case [116].

Chemokines and Cytokines: Major Determinants of Leukocyte Accumulation

The specific leukocyte subsets recruited to sites of renal inflammation are guided by the combination of chemokines and cytokines present, which all resident cells, including microvascular endothelial cells, **podocytes, tubular, and mesangial cells**, have the capacity to produce. Chemokines are associated with renal injury in human GN, such as IgA nephropathy, membranoproliferative or **crescentic GN** [10], as well as in mouse models, and appear to play a central role in disease pathogenesis (reviewed in [11]). The primary inflammatory trigger and nature of the initial damage dictates the type and extent of local cytokines produced and, in turn, the type of leukocytes recruited (e.g., ischemia, toxin exposure, pathogen invasion, immune complex deposition or formation, as well as dysregulation of proinflammatory pathways and complement, etc.).

Glossary

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV): vasculitis induced by the production of auto-antibodies (ANCA) directed against neutrophil granule proteins.

Crescentic glomerulonephritis: a form of severe GN observed in various disorders (e.g., lupus nephritis, ANCA-associated GN) that is morphologically characterized by crescent formation in the urinary space (Bowman's space) resulting from the rupture of the glomerular capillary wall and the effusion of plasma molecules, with subsequent fibrin formation and efflux of macrophages and T cells, leading to cellular and/or fibrous proliferation inside the urinary space.

Diabetic nephropathy: kidney disease caused by type 1 or type 2 diabetes, with characteristic glomerular changes including mesangial expansion and glomerular sclerosis.

Focal segmental glomerulosclerosis (FSGS): a form of glomerular disease characterized by a focal (involving only some glomeruli) and segmental (only a portion of the glomerulus) glomerular sclerosis, which can be idiopathic or secondary to infections, drugs, or toxins.

Glomerulonephritis (GN): inflammatory disease of the kidney primarily involving the glomeruli.

Hypertensive nephropathy: kidney disease caused by chronic hypertension characterized by vascular damage including glomerular arteries that leads to glomerulosclerosis and tubulointersitial fibrosis.

Lupus membranous nephropathy: a form of lupus nephritis (also termed class V lupus nephritis) characterized by subepithelial immune-complex deposition leading to diffuse thickening of the glomerular basement membrane.

Neutrophil extracellular traps (NETs): nuclear chromatin fibers that contain immunostimulatory proteins and autoantigens

Podocytes, mesangial, and tubular cells: podocytes are specialized epithelial cells forming the visceral sheet of the urinary space (Bowman's space) of the glomeruli and the main component of the glomerular barrier; mesangial cells are

Key Figure

Mechanisms Controlling Leukocyte Accumulation During Kidney Inflammation

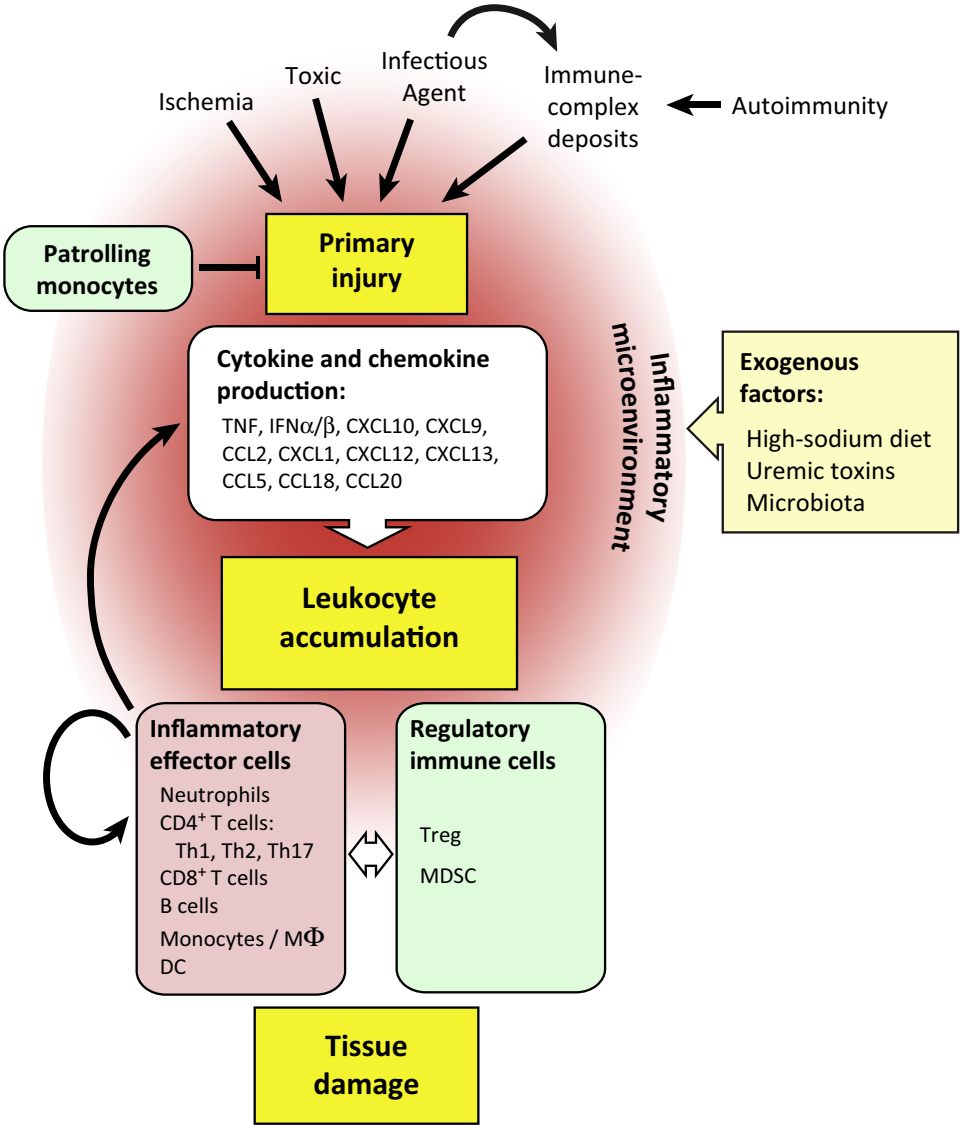

Figure 1. Various triggers induce primary renal tissue injury that subsequently leads to the production of cytokines and chemokines from intrinsic renal cells. These inflammatory cues, dictated by the nature and the site of the initiating injury, coordinate leukocyte accumulation and the temporal infiltration of leukocyte subsets. Recruited leukocytes, in turn, influence the recruitment and activation of other immune cells as well as the responses from renal cells. Recruited immunoregulatory cells eventually terminate the inflammatory response. Patrolling monocytes may also control inflammatory responses by maintaining endothelial integrity. Finally, the inflammatory microenvironment, influenced by exogenous factors such as high-sodium diet, uremic toxins, and microbiota (see text), define the inflammatory landscape and thus leukocyte influx. MΦ, macrophages.

specialized smooth muscle cells surrounding the glomerular capillaries; tubular cells are specialized epithelial cells delineating the renal tubules.

Pyelonephritis: infection of the kidney.

Tubulointerstitial nephritis: kidney disease primarily characterized by inflammation of the tubulointerstitial compartment of the kidney.

Uremic toxins: retained solutes accumulating when the glomerular filtration rate is reduced in chronic kidney disease (CKD) and which contribute to the systemic symptoms of renal failure.

Generally, chemokines binding to CXCR3, CXCR6, CCR5, or CX3CR1 recruit Th1 cells that locally produce type 1 cytokines (IL-2, IFN-γ), whereas chemokines engaging CCR3, CCR4, or CCR8 recruit Th2 cells and eosinophils. In chronic GN, CXCR3-binding chemokines, including CXCL10 (IP-10) and CXCL9 (Mig), are of special interest. They sustain the recruitment of CXCR3-bearing Th1 cells and macrophages in murine models of immune complex-induced nephrotoxic nephritis and in lupus nephritis models [12–14]. In humans, high expression levels of CXCL10 and CXCL9 have been reported in resident glomerular cells in kidney biopsies of patients with membranoproliferative and crescentic GN [15]. Furthermore, high urinary excretion of CXCL9 and CXCL10 has been associated with systemic lupus erythematosus (SLE) kidney involvement [16,17]. Th17 cells, elicited via CCR6 and Th1 cells, play a prominent role in kidney inflammation (reviewed in [18,19]), and they also express CXCR3. Therefore, CXCR3-binding chemokines can recruit both Th1 and Th17 polarized cells. Th17 production of IL-17 can in turn induce the production of CCL2 by renal intrinsic cells, leading to macrophage recruitment [14]. Because both Th1 and Th17 play important roles in glomerular inflammation, and share similar recruitment cues, their interactions have been further explored in the murine nephrotoxic nephritis model. Th17 cell accumulation is an early event during the adaptive immune response induced in the nephrotoxic nephritis mouse model (autologous phase), and these cells might be the major source of IL-17 responsible for neutrophil recruitment and renal damage. Th17 induction of local CXCL9 expression results in Th1 recruitment and IFNγ production, with subsequent macrophage and dendritic cell (DC) accumulation, thus extending kidney damage. IFN-γ production inhibits CCL20 production and further enhances Th17 cell recruitment [20]. A recent report indicated that pathogenic Th17 cells recruit neutrophils through upregulation of CXCL5 expression in kidney tubular cells following the induction of nephrotoxic nephritis. CXCL5 deficiency or blockade significantly reduced neutrophil accumulation and kidney damage. Notably, the Th17/IL-17–CXCL5 axis was not involved in bacterial clearance after **pyelonephritis**, suggesting that it was specifically engaged in sterile inflammation, as is the case in autoimmune pathology [21]. It is possible that initial Th17 recruitment is driven by kidney DC chemokines because their depletion before unilateral ureteral obstruction (UUO mouse model) attenuates both Th1 and Th17 cell accumulation [22]. CXCL13, locally produced by infiltrating DCs, appears to be another major pathogenic chemokine in (NZB/W) F_1 mice, a murine model of lupus nephritis [23]. This may have relevance in humans because high serum levels of CXCL13 have been associated with SLE nephritis [24,25]. *In vitro*, CXCL13 engagement via CXCR5 on podocytes leads to the secretion of proinflammatory molecules such as CXCL1, CXCL12, and macrophage inhibitory factor (MIF) which can prime the oxidative burst in isolated human neutrophils [23], a possible means of amplifying glomerular inflammation.

More recently, CCL18 was identified as a central chemokine in orchestrating inflammation and tissue damage specifically in human **anti-neutrophil cytoplasmic antibody (ANCA)-associated crescentic GN** [26]. Immunohistochemistry revealed high levels of CCL18 expressed by macrophages and myeloid DCs in patient biopsies. CCL18 serum levels were also significantly elevated in patients with **ANCA-associated vasculitis (AAV)**, both at the time of diagnosis and during relapses. Engagement of CCL18 via CCR8 might promote lymphocyte and monocyte recruitment. However, CCL18 does not have a murine equivalent, precluding its study in murine models. Nevertheless, CCR8 is expressed in mice and binds to CCL1 and CCL8, the latter being a functional analog of CCL18. In the nephrotoxic nephritis murine model, CCR8 was shown to drive the recruitment of mononuclear phagocytes [26]. In addition to CCL18, many other chemokines have also been identified in biopsies of AAV patients, including CCL5, CXCL9, CXCL10, and CCL20 [26], suggesting that CCL18 functions within a complex array of proinflammatory chemokines. Given the prominent role of CCL18 in AAV, it will be of interest to elucidate its importance in other forms of GN.

Box 1. TNF and Kidney Inflammation

TNF is found both as a soluble and membrane-anchored form that differentially activate the two TNF receptors, TNF receptor 1 and 2 (TNFR1 and TNFR2, respectively); only the membrane-bound form has significant affinity for TNFR2 [28,109]. Soluble TNF, which favors TNFR1 engagement, orchestrates a proinflammatory cascade in microvascular endothelial cells by inducing the generation of interferon beta (IFNβ) which binds IFNα/β receptor (IFNAR) in an autocrine manner, thus triggering the production of CXCR3 chemokines (e.g., CXCL9 and CXCL10) that support monocyte recruitment. Both TNFRs are required for interferon regulated factor-1 (IRF1)-dependent IFNβ production and, *in vivo*, support macrophage accumulation following acute inflammation induced by the injection of soluble TNF. However, in a model of NTN, where TNFR2 could be engaged by membrane-bound TNF presented by recruited neutrophils, TNFR2 and not TNFR1 was essential for macrophage accumulation [108,109]. Notably, a central role for CXCR3-binding chemokines CXCL10 and CXCL9 has been demonstrated in the nephrotoxic nephritis model [12,13]. Thus, although circulating soluble TNF is traditionally identified as a hallmark of systemic inflammation, its local production and subsequent generation of IFNβ via an autocrine loop likely shapes the inflammatory environment in the kidney. Hence, the pathogenic consequences of TNF are likely influenced by the relative abundance of TNFR1 versus TNFR2 and by the extent to which TNF sheddases (e.g., ADAM17) [110] are present, dictating the amount of membrane-bound versus soluble forms of TNF available. TNFR2 is significantly upregulated in endothelial cells and podocytes following glomerular inflammation induced by TNF injection or nephrotoxic nephritis in mice, as well as in renal biopsies from patients with acute renal allograft rejection and ischemic kidney injury (acute tubular necrosis) [108,109,111,112]. Inducible expression of TNFR2 at the transcriptional level might be regulated by mediators that increase intracellular cAMP levels, or that induce the transcriptional activation of NF-**κB, AP-1, IRF**, or GAS, because consensus sites for these factors are present within the TNFR2 promoter [108,113]. Thus, control of TNFR2 expression may serve as an additional regulatory point for TNF-mediated leukocyte recruitment.

The role of TNF in kidney inflammation is particularly illustrative of the complex interactions between immune effector cells and kidney intrinsic cells driving local chemokine generation (Box 1). In the GN animal model, the main source of TNF comes from intrinsic renal cells, and TNF itself promotes kidney injury [27,28]. In addition, TNF is a potent cytokine that further enhances the inflammatory response. Nevertheless, despite a prominent role for this pleiotropic cytokine in kidney inflammation, anti-TNF treatments have failed to show a clear benefit over standard immunosuppressive treatments of GN, notably in ANCA-associated GN [28]. This may be explained by the various roles of TNF in promoting inflammation (e.g., inducing immune cell recruitment) but also in resolving inflammation (e.g., apoptosis of immune cells), as well as in immunomodulation. The importance of TNF in immunomodulation is highlighted by findings in patients with inflammatory diseases where TNF blockade has been reported to induce antibodies against double-stranded DNA (dsDNA), and occasionally lupus-like syndromes [29–31]. Thus, a more targeted approach that specifically neutralizes the proinflammatory role of TNF while leaving its other functions intact may represent a more promising therapeutic strategy.

In addition to recruitment, the retention of effector T cells at sites of inflammation appears to contribute to disease pathogenesis in different organs. For instance, recent mouse studies have shown that the antigen-dependent activation of effector T cells *in situ* by tissue-resident antigen-presenting cells can result in T cell accumulation in various inflamed tissues. An absence of such interactions led to increased T cell exit via afferent lymphatics and accumulation in draining lymph nodes [32,33], guided by CCR7–CCL19/21 chemokine receptor/ligand cues [32,34]. Deletion of a scaffold protein, AKAP9, important in TCR recycling has also been shown to impair *in situ* T cell reactivation and to increase effector T cell egress to draining lymph nodes, concomitant with reduced kidney injury in mouse models of nephrotoxic nephritis (NTN) [35].

Roles of Leukocyte Subsets in Kidney Disease

Different subsets of leukocytes are involved in distinct and overlapping aspects of the immune response. First on site, neutrophils are able to quickly eliminate invading pathogens. They also communicate with other immune cells and participate in inflammation, as in the case of chronic GN [36,37]. There is mounting evidence that neutrophils are key players in SLE pathogenesis [38] that is associated with renal injury both in pediatric and adult SLE [37,39–41], as well as in mouse models of lupus nephritis [42,43]. Moreover, a distinct population of lupus patient neutrophils has been identified, and these low density granulocytes cosegregate with

Box 2. Tissue Microenvironment Influences on Immune Cell Phenotypes

The tissue environment itself very likely impacts on immune cell phenotypes. Gene transcription analyses of various subsets of resident macrophages (brain microglia and resident peritoneal macrophages) have revealed that the tissue microenvironment can have a large impact on the transcriptional profile of the cell. That is, a common enhancer landscape combined with tissue specific 'superenhancers' has been shown to determine the phenotype of tissue-specific resident macrophages [114]. Although not yet fully supported, the transcriptional profile of immune cells recruited during an inflammatory response could likewise be fundamentally influenced by tissue-intrinsic factors in addition to inflammatory mediators. For example, infiltrating T cells following renal ischemia–reperfusion injury (IRI) in mice have shown a marked change in gene transcription as early as 6 h after injury [115]. As such, CCR5 upregulation has been suggested to be particularly prominent and functionally relevant to renal disease pathophysiology [115].

mononuclear cell fractions [44,45]. Compared to normal neutrophils, this subset has a heightened capacity to induce vascular damage, synthesize granule proteins such as MPO and MMPs, express proinflammatory molecules, and form **neutrophil extracellular traps** (NETs) [39,46].

In terms of recruitment, phagocytic mononuclear cells (including monocytes, macrophages, and DCs), B cells, and different T cell subsets are likely to play important roles in the pathogenesis of renal diseases, but full supportive evidence remains to be accumulated in this arena.

Exogenous Factors Influencing the Inflammatory Microenvironment

In addition to inflammatory molecules, the tissue environment itself might have an impact on immune cell phenotypes (Box 2). Along these lines, a change in the intrinsic renal milieu by exogenous environmental stimuli to which the kidney is particularly susceptible may have a strong influence on immune cell phenotypes, and thus on the overall inflammatory landscape.

Sodium

NaCl levels, highly relevant to kidney disease, have recently been shown to modulate the inflammatory microenvironment. Intriguing data from two independent groups [47,48], have suggested that increasing concentrations of NaCl (10–40 mM) induced a strong Th17 phenotype in naïve $CD4^+$ cells in a dose-dependent manner. This effect was sodium-dependent because it was reproducible with sodium gluconate but not with $MgCl_2$. Th17 induction was also dependent on SGK1, p38/MAPK, and NFAT5 [47]. The biological significance of this observation was confirmed *in vivo* in a mouse model of multiple sclerosis, where: mice on a high-salt diet exhibited an accelerated onset and increased severity of disease [47,48]. Similar results were observed in a murine model of chronic heart allograft rejection: a high-salt diet accelerated graft rejection in mice [49]. Thus, the mechanistic role of sodium in kidney disease pathogenesis may represent a fruitful area of investigation.

Uremic Toxins

GN is the third cause of chronic kidney damage leading to reduced glomerular filtration rate and the accumulation of **uremic toxins**, as in chronic kidney disease (CKD). CKD by itself is linked to some form of chronic systemic inflammation that is poorly characterized and might further contribute to kidney damage and ESRD. Enhanced oxidative stress in CKD due to uremic toxins can lead to tissue damage and the secretion of DAMP (damage-associated molecular pattern) molecules that activate pattern recognition receptors, such as Toll-like receptors (TLRs), during the innate immune response [50,51]. *In vitro*, the uremic toxin indoxyl sulfate has been shown to increase LPS-induced macrophage activation (increased protein expression of COX2, iNOS, as well as production of NO, TNF, and IL6) [52]. In addition, analysis of stimulated peripheral T cell supernatants from CKD stage 4 patients has indicated a higher production of cytokines such as TNF, IL-10, IL-12, IL-15, IL-8, MCP-1, CXCL10, IFN-α2, IL-1α, and eotaxin relative to controls [53]. Transcriptional profiling of circulating monocytes from CKD patients has also suggested dysregulated signaling in the Wnt/β-catenin pathway, possibly contributing to enhanced inflammation through increased monocyte adhesion and IL-6 production [54]. Uremic toxin

accumulation has thereby the potential to alter significantly both innate and adaptive immune responses. Nonetheless, little mechanistic data are currently available to elucidate the effect of the uremic environment *per se* on the immune system.

Microbiota

Alteration of the normal intestinal microbiome (or intestinal dysbiosis) has been previously associated with SLE [55]. This in turn may influence the development of IgA nephropathy [56]. In mice, transgenic overexpression of BAFF, a B cell stimulating factor, has been shown to lead to the development of high circulating levels of IgA which are associated with IgA mesangial deposition and nephritis [57]. Commensal bacteria-reactive IgA was produced in these mice, suggesting that the intestinal microbiota participates in autoimmune IgA nephropathy in this animal model [57]. Related to this, at steady-state, the microbiota was shown to limit the transport of bacteria from the lumen to mesenteric lymph nodes (MLNs). However, upon breakdown of these conditions (as in antibiotic-induced dysbiosis), non-invasive bacteria were transported to the MLNs via CX3CR1^{+} phagocytes, triggering both IgA production and T cell responses [58]. In humans, a genome-wide association study (GWAS) of IgA nephropathy patients identified new genomic loci, which included genes involved in intestinal epithelial barrier maintenance and in immune responses to mucosal pathogens (*DEFA, TNFSF13, VAV3, ITGAM/ITGAX, PSMB8*) [59]. Thus, alterations in host–intestinal pathogen interactions may increase susceptibility to IgA nephropathy.

Effector and Regulatory Immune Cells and the Renal Inflammatory Response

Regulatory Immune Cells

In the past two decades significant strides have been made in understanding the mechanisms that restrict inflammation and maintain immune homeostasis. In particular, anti-inflammatory or immunoregulatory cell subsets belonging to the T cell and monocyte cell lineages have been demonstrated to play a major role in controlling autoimmunity and resolving inflammation.

Regulatory T cells

Regulatory T cells (Tregs) are a subset of CD4^{+} T cells that express the transcription factor Foxp3 and, through production of IL-10, exhibit numerous anti-inflammatory properties that fundamentally contribute to immune homeostasis [60]. Tregs have an important protective role in kidney inflammatory diseases. In mouse models, Treg impairment has been associated with exacerbated disease in cisplatin-induced nephrotoxicity [60], nephrotoxic nephritis (NTN) [61–66], anti-myeloperoxidase GN [67], and acute ischemic kidney injury [68–70]. Furthermore, adoptive transfer of Tregs before the induction of nephrotoxic nephritis significantly decreased kidney damage [71]. In response to nephrotoxic nephritis, Treg expression of CCR6 and CCR7 was required for their proper recruitment to the kidney, and deficiency of either of these chemokine receptors was associated with worsened disease [62,63]. Treg production of IL-10 appeared to be central in limiting the extent of GN disease, at least in part, by reducing the accumulation of IFNγ^{+}, IL-17^{+}, and double-positive IFN-γ^{+}/IL-17^{+} CD4^{+} T cells [61]. In an NTN model, Tregs were recruited to the kidney through Stat3-dependent expression of CCR6. Specific depletion of Tregs expressing Stat3 (Foxp3^{Cre}/Stat3$^{fl/fl}$ mice) resulted in more severe glomerular and interstitial damage [65]. Indeed, these data highlight how Tregs can modulate a variable set of transcription factors and surface phenotypes to target disease-specific immune responses, including that of Th17-mediated kidney damage [72].

The observed roles of Tregs in mouse models might extend to humans. For instance, decreased Treg numbers have been shown to be associated with human renal disease; as such, Foxp3^{+} T cells numbers in kidney biopsies might predict renal survival in patients with ANCA-associated vasculitis [73]. In SLE patients, reduced numbers of peripheral blood Tregs have been observed [74], and a lower ratio of peripheral blood Treg/Th17 has been associated with lupus nephritis

and inversely correlated with the overall clinical severity of SLE [75]. In kidney biopsy samples from patients with active proliferative lupus nephritis and ANCA-associated vasculitis, the ratio of $FoxP3^+/CD3^+$ cells was significantly lower compared to hypertensive nephropathy, **lupus membranous nephropathy** (class V), and **tubulointerstitial nephritis** [76]. The change in Treg numbers in lupus may be a consequence of the reduced IL-2 levels observed in SLE patients because this cytokine plays an important role in Treg development and survival [77]. Indeed, the spontaneous autoimmune manifestations detected in IL-2-deficient mice might be associated with the large reduction in Tregs numbers found in the periphery [77].

Myeloid-Derived Suppressor Cells (MDSC)

MDSCs, a heterogeneous population of myeloid progenitor cells and immature myeloid cells, contribute to immune homeostasis through their potent T-cell-suppressive abilities. In mice, they are characterized by the surface expression of integrin CD11b, together with mouse myeloid cell lineage surface markers Ly6C (monocytic morphology) and Ly6G (granulocytic morphology), and in humans by the expression of CD14 ($CD14^+$ $CD16^-$ cells) or both CD14 and CD16 ($CD14^+/CD16^+$). Their trafficking is mainly dictated by the chemokine receptor CCR2 [78,79]. They are found in mouse models of rheumatoid arthritis, diabetes, and multiple sclerosis (EAE). Peripheral blood naïve monocytes ($CD11b^+$ $Ly6G^-$) also display *in vitro* intrinsic suppressive properties by inhibiting T cell proliferation through a mechanism that requires cell–cell contact and, partially, nitric oxide (NO) production [80].

The biological relevance of MDSC is inferred from murine models as well as from clinical observations. In the kidney, MDSCs were found to accumulate in an allograft model in rats, inhibiting both proliferation and induced apoptosis of alloreactive T cell through a NO-dependent mechanism [81]. More recent work has shown increased numbers of circulating MDSC in kidney allograft transplant recipients, correlating with higher numbers of Tregs in the circulation [82]. In addition, isolated MDSC from kidney transplant recipients were capable of inhibiting $CD4^+$ T cell proliferation as well as of inducing the expansion of $Foxp3^+$ Tregs *ex vivo* [82]. Finally, glucocorticoid treatment of patients with **focal segmental glomerulosclerosis** (FSGS) induced a rapid increase in MDSCs in peripheral blood, which appeared to be predictive of individual clinical responses [83]. In a corresponding proteinuria mouse model of doxorubicin-induced renal injury, MDSC depletion using an anti-Gr-1 antibody (although not fully specific) abolished the protective effect of glucocorticoids, while the adoptive transfer of MDSC appeared to be protective by inducing the proliferation of $CD4^+$ $CD25^+$ $FoxP3^+$ cells and by reducing the number of $CD11c^+$ and $F4/80^+$ cells in the kidneys [83].

Patrolling Monocytes

Patrolling monocytes exhibit a characteristic slow motion at the surface of endothelia, following complex tracks, including U-turns and spirals, as assessed by IVM [84,85]. Their molecular phenotype is characterized by the high surface expression of the adhesion-related receptor CX3CR1, together with low expression of CD14 in human ($CD14^{dim}$) and $Ly6C^-$ in mice. After phagocytosis of apoptotic cells, patrolling monocytes express high levels of PDL-1 and thereby suppress antigen-specific T cell responses in the spleen [86]. In the context of inflammation, they can be retained in kidney capillaries and mediate neutrophil recruitment, followed by focal and contained necrosis of endothelial cells and scavenging of cellular debris within the capillary lumen [87]. $CD14^{dim}$ monocytes also specifically target viruses through TLR7 and TLR8, and are able to produce high levels of proinflammatory cytokines such as TNF, IL-1β, CXCL10, and CCL5 [88]. In lupus nephritis, their protective function may therefore be ambiguous because immune-complex deposition containing self-nucleic acids in the glomeruli may trigger a proinflammatory response of patrolling monocytes by engaging TLRs. The human relevance of potentially protective CX3CR1-bearing cells is suggested by the reduced risk of acute kidney injury (AKI) during sepsis of patients expressing the I249 CX3CR1 polymorphism, which functionally

increases CX3CR1-mediated monocyte binding to CX3CL1, its cognate ligand [89]. Thus, patrolling monocytes appear to play an important function in maintaining endothelium integrity and thus potentially, immune homeostasis. Of note, CX3CR1 is also expressed on $CD11c^+$ DCs recruited to the kidney cortex during NTN, an immune-complex-mediated disease. Hence, as opposed to DC-independent ischemic or obstructive kidney injury models, CX3CR1-expressing DCs appear to promote kidney inflammation and tissue damage in NTN [90].

Plasticity of Regulatory Cells

IL-17 expressing Treg (Treg17) cells displaying a proinflammatory phenotype have also been reported in various inflammatory conditions [87,91]. In view of the great diversity of $CD4^+$ T cells and the various adaptive mechanisms that have been observed, some aspects of lineage commitment and full determination are being questioned, and the plasticity of Tregs versus the paradigm of stable, terminally differentiated Th cells is now gaining acceptance [92]. The local microenvironment in which the $CD4^+$ T cell is recruited may contribute to determine its fate as well as the stability of its immunophenotype. Indeed, there are many examples of transient or unstable expression of Th-specific transcription factors, notably Foxp3 [93,94]. A recent study demonstrated that TNF inhibition in patients with rheumatoid arthritis increased the number of peripheral Th17 cells with regulatory properties because these cells expressed high levels of IL-10 in a Foxp3-independent manner [95]. This suggests that alterations in the proinflammatory milieu can affect the phenotype and function of Th17 effector cells in humans.

Further complexity is introduced by the recent identification of another subset of Tregs, termed bifunctional Treg or biTreg, that express both Foxp3 and RORγt, a Th17 transcription factor; accordingly, the cells are able to produce IL-17 [96]. Their role in renal inflammatory disease was recently explored in the murine NTN model [97]. In this study, biTregs expressing both IL-10 and IL-35, as well as proinflammatory IL-17 cytokines, appeared to be distinct from Treg17 and did not derive from or transdifferentiate into either Tregs or Th17. On the one hand, adoptive transfer of biTregs suppressed renal proinflammatory cell infiltration but, on the other hand, biTregs produced RORγt-dependent-IL-17 and participated in glomerular damage [98]. Thus, biTregs appeared to contribute to both inflammatory damage as well as immunoregulation in this murine model. Although the specific function of this novel bifunctional T cell subpopulation in kidney inflammation remains elusive, the data exemplify the complex interchange between proinflammatory and regulatory immune cells.

Towards Better Targeted Anti-inflammatory Treatments

Cumulative knowledge of cytokines and chemokines in various inflammatory diseases has led to the development of new drugs in the past decade, predominantly blocking antibodies, to target key inflammatory mediators. Some have reached the clinic with great success but also with some disappointments. Given the multifaceted and/or redundant roles of cytokines, identifying the right targets in disease has proved to be difficult. Indeed, in some cases, modulating the immune response using biologics has produced unexpected results. For instance, potent anti-inflammatory drugs such as TNF inhibitors have been associated with adverse autoimmune manifestations such as drug-induced lupus [28,99,100]. Anti-TNF drugs induce a shift in production of anti-inflammatory cytokines (particularly IL-10), which may lead to cytokine imbalance, autoantibody production, and/or autoimmune manifestations in susceptible individuals [99]. In addition, apoptosis of immune effector cells induced by such treatments may release auto-antigens that may further stimulate autoantibody production [99]. The monoclonal anti-IL-6 receptor blocking antibody tocilizumab has shown great efficacy in the treatment of severe RA [101], but yet exacerbated kidney damage in the NTN mouse model [102]. In this study, IL-6 inhibited the proliferation of splenic proinflammatory macrophages expressing high levels of IL-6Rα. This might suggest a novel (and clinically relevant) immunoregulatory function for IL-6 [102], as has been reported in cases of psoriasis and in one case of immune complex mediated

GN where patients were treated with tocilizumab [103,104]. Targeting IL-17 has also been proposed to treat many autoimmune diseases. However, in IL-17A-deficient MRL/*lpr* lupus mice, or in NZB/NZW lupus mice treated with anti-IL-17A, lupus-induced nephritis was not prevented [98]. Further studies are still necessary to fully evaluate the benefit and safety of anti-IL-17 treatments in autoimmune diseases.

Novel therapeutic approaches are also aimed at enhancing Treg responses to control inflammation and prevent autoimmunity. Adoptive transfer of expanded Tregs *ex vivo* has shown some promising results in animal models, and notably in a lupus nephritis model [105]. Another strategy has been to pharmacologically enhance Treg recruitment using *N,N*-dimethylsphingosine, and this has shown some benefit in a mouse model of ischemia–reperfusion induced kidney damage [106]. Phase I clinical trials are currently ongoing to test the therapeutic potential of autologous adoptive transfer of *ex vivo* expanded Tregs in kidney transplantation [107] and in lupus nephritis, among other conditions (see http://clinicaltrials.gov). Nevertheless, such strategies are challenging; for instance, the maintenance of a regulatory immunophenotype requires a specific molecular signature and a combination of transcriptional factors. A proinflammatory milieu may also guide the Treg suppressive phenotype towards a proinflammatory one. Therefore, in the clinic, one difficulty (among many) will be to sustain the regulatory phenotype of transferred Tregs. We speculate that this will require further pharmacological interventions or genetic reprogramming such that switching between regulatory and proinflammatory cellular phenotypes is disabled. This will clearly warrant further experimentation and insight.

Outstanding Questions

How do inflammatory molecules interact with kidney-intrinsic cells to generate chemokines?

What are the molecular cues and pathways that support the recruitment of different immune cells in the glomeruli and interstitium, and do these differ depending on the stimulus?

What are the local renal factors that sustain the recruitment as well as maintain the regulatory phenotype of Tregs?

Do *ex vivo* Treg conditioning and adoptive transfer methods represent an efficient therapeutic strategy for the treatment of kidney inflammation in humans?

What are the molecular pathways by which exogenous factors impact on renal inflammation? Some of these factors could include changes in sodium levels, microbiota, uremic toxins, or other.

Concluding Remarks

The changing landscape of renal inflammation is dictated by the secretion of proinflammatory molecules from tissue-resident cells, amplified by the recruitment of immune effector cells, and modulated by both regulatory and effector cell populations. This complex set of interactions and processes appears to continuously evolve during the course of an inflammatory response; the relative contribution of each results in either the escalation or resolution of inflammation. Although progress has been made in understanding these processes in the context of kidney inflammation, a greater understanding of the local renal-specific inflammatory microenvironment and its influence on the heterogeneity and plasticity of immune effector and regulatory cells is urgently needed (see Outstanding Questions). Moreover, the molecular pathways that promote leukocyte recruitment in the specialized microvasculature of the kidney in response to various inflammatory stimuli need to be further delineated. Future investigations into the conditions that enable an immunosuppressive microenvironment in the kidney are also warranted. These types of studies may lead to the identification of therapeutic targets to fine-tune the inflammatory microenvironment in the kidney such that the recruitment and function of effector cells may be suppressed while at the same time the participation of regulatory cells may be enabled. This type of local immunoregulatory calibration may indeed represent the type of scalpel approach necessary to reduce the burden of ESRD due to inflammation, while ideally minimizing the risk of global immunosuppression.

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