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