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The immunoregulatory roles of non-haematopoietic cells in the kidney

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Abstract

The deposition of immune complexes, activation of complement and infiltration of the kidney by cells of the adaptive and innate immune systems have long been considered responsible for the induction of kidney damage in autoimmune, alloimmune and other inflammatory kidney diseases. However, emerging findings have highlighted the contribution of resident immune cells and of immune molecules expressed by kidney-resident parenchymal cells to disease processes. Several types of kidney parenchymal cells seem to express a variety of immune molecules with a distinct topographic distribution, which may reflect the exposure of these cells to different pathogenic threats or microenvironments. A growing body of literature suggests that these cells can stimulate the infiltration of immune cells that provide protection against infections or contribute to inflammation – a process that is also regulated by draining kidney lymph nodes. Moreover, components of the immune system, such as autoantibodies, cytokines and immune cells, can influence the metabolic profile of kidney parenchymal cells in the kidney, highlighting the importance of crosstalk in pathogenic processes. The development of targeted nanomedicine approaches that modulate the immune response or control inflammation and damage directly within the kidney has the potential to eliminate the need for systemically acting drugs.

Introduction

Kidney inflammation is associated with a variety of entities, including diseases such as lupus nephritis and vasculitis, and injury, for example, following ischaemia–reperfusion or kidney transplantation. Invariably, such inflammation exacerbates kidney damage and can lead to kidney failure. In the case of lupus nephritis and vasculitis, kidney inflammation is driven by autoimmunity. Multiple pathogenic pathways, involving genetic, epigenetic, hormonal, environmental and immunoregulatory factors, contribute to the development of autoimmunity[1]. However, not all patients with features of autoimmunity develop organ

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damage, suggesting a role for local factors in organs such as the kidney. Indeed, emerging evidence suggests that cells resident within organs can facilitate the instigation and propagation of tissue injury through a variety of processes[2]. The importance of these resident cells to disease processes is highlighted by the finding that the inhibition of kidney parenchymal cell (KPC) function can in some instances attenuate kidney damage, even in the presence of rampant peripheral humoral and cellular autoimmune responses[3,4].

Systemic autoimmune diseases involve multiple elements and pathways of the innate and adaptive immune systems[5-7]. In systemic lupus erythematosus (SLE), autoantibodies form immune complexes with autoantigens, such as nucleosomes in the circulation, which can subsequently deposit in tissues, including the glomerular basement membrane[8-10]. The excessive production of cytokines, including type I interferon (IFN), IL-6, IL-17 and IL-23 by immune cells further induce immune cell abnormalities and can directly damage KPCs[4]. Moreover, autoreactive T cells, the antigen specificity of which is yet to be defined, infiltrate the kidney where they can form tertiary lymphoid organs (TLOs) that also contribute to the development of organ damage[11,12]. Precisely how infiltrating immune cells contribute to the demise of KPCs remains unclear, but may involve direct cell cytotoxic effects or the release of cytokines and chemokines that may alter the metabolism and/or functions of KPCs.

The prevailing belief is that the deposition of autoantibodies or immune complexes in the glomerulus or other parts of the kidney triggers and sustains an inflammatory response, resulting in kidney injury[13]. This assumption implies that once the peripheral autoimmune response is established, it will cause kidney damage without any contribution from the KPCs. However, this assumption is challenged by the observation that not all patients with anti-nuclear antibodies or antibodies to DNA develop clinically apparent lupus nephritis[14]. Furthermore, the assumption that circulating cytokines act on cells of the immune system to induce an inflammatory response has driven the development of biologics that inhibit cytokines, such as IL-6, IL-17 and IL-23, that are present in the sera of patients with autoimmune disease[15,16]. However, the fact that these cytokines might also directly affect KPCs to alter their metabolism and/or function has not generally been considered. Thus, despite the recognized association between kidney inflammation and morbidity and mortality[13,17], it remains unclear whether peripheral autoimmunity alone – that is, the presence of autoantibodies, immune complexes and autoreactive immune cells–is sufficient to induce kidney injury.

A growing body of evidence suggests that molecular processes within the kidney parenchyma are needed for the demise of kidney tissue. This notion is in line with the idea of ‘structural immunity’, whereby non-haematopoietic, tissue-resident cells can adopt the tissue-specific and regulated expression of genes involved in immune functions[18]. Comprehensive characterizations of non-haematopoietic cells have demonstrated the regulation of such immune genes under physiological conditions and in response to viral infections[18]. This Review is aimed at providing critical discussion of the emerging information in support of the notion that KPCs provide structural immunity to the kidney by upregulating or altering the expression of immune-related genes, which in turn contributes to the infiltration of immune cells and exacerbates kidney injury.

Immune cells in the kidney

Inflammation of the kidney (nephritis) is a feature of various clinical entities, including systemic autoimmunity, vasculitis, transplantation and ischaemia–reperfusion injury[19]. Regardless of the aetiology, the immune response in the kidney involves the release of soluble inflammatory mediators such as cytokines and chemokines, the recruitment of immune cells and the activation of resident immune cells. These processes alter the metabolism and expression of genes that may contribute to sustenance of the inflammatory process[20].

In patients with kidney disease, the accumulation of immune cells in the tubulointerstitium is strongly associated with an increased risk of progression to kidney failure[21-23]. However, the fact that not every patient with tubulointerstitial inflammation develops kidney failure[21,23] suggests heterogeneity in the inflammatory response, which may underlie the diversity in outcomes[24]. Thus, better understanding of the types of infiltrating immune cells, their behaviour and their location in the kidney may provide important insights into the mechanisms that drive the progression of kidney injury in particular patients.

Cells of the innate immune response

Various components of the innate immune response have been implicated in the progression of kidney diseases. Mononuclear phagocytes, including tissue-resident macrophages, type 1 classic dendritic cells (cDC1s), type 2 classic dendritic cells (cDC2s) and plasmacytoid DCs, exist in healthy kidneys where they reside near the periphery of glomeruli or peritubular capillaries[25-27]. During kidney inflammation, a number of these cells expand, primarily in the tubulointerstitial area and in the periglomerular area[21,28] (Fig. 1). These cells can demonstrate an activated phenotype, characterized by the production of cytokines including IFNα, or assume a “reparative” phenotype to facilitate the elimination of debris and suppress inflammation[28]. Mixed populations of phagocytic cells also infiltrate the kidney, further propagating the inflammatory response. It is important to note that some infiltrating phagocytes, such as cDC1s, have a protective role[25,28]. Similarly, infiltrating and resident macrophages in the kidney can adopt an alternatively activated reparative phenotype and can function to remove cell debris, suppress inflammation and promote the regeneration of injured tubular epithelium[29,30]. However, little is known about the core transcription factors that regulate renal phagocyte fate and function. In addition, other immune cell types, including natural killer (NK) cells, γδ T cells and innate lymphoid cells have been identified in kidneys from patients with lupus nephritis[31,32], although the exact role of these cells in kidney injury are unclear. Importantly, the intrinsic characteristics of innate lymphoid cells are key to maintaining the homeostasis of the innate and adaptive immune response, as well as the bidirectional interactions with organ resident cells[33,34].

Cells of the adaptive immune response

The adaptive immune system – comprising T lymphocytes and B lymphocytes – also has an active role in kidney inflammation and injury. Infiltrating lymphocytes accumulate mostly in the interstitial region rather than in the glomeruli, where they form clusters with each other and other immune cells[35]. Interestingly, some of these clusters display features of

secondary lymphoid organs, including the presence of T cell and B cell zones that align with newly formed high endothelial venules (HEVs) and lymphatic vessels, and are known as TLOs[35-37] (Fig. 1). TLOs are defined as lymphoid aggregates with organized stromal components consisting of follicular dendritic cells and fibroblastic reticular cells (FRCs). Remarkably, the formation and maintenance of TLOs requires molecular mechanisms, that is, lymphotoxin and lymphoid chemokines, which are very similar to those required of the formation of secondary lymphoid organs[38]. These structures can harbour pro-inflammatory, pathogenic lymphocytes that sustain local inflammation, but can also contain cells that provide tissue protection by restraining the magnitude of the inflammation[35]. Better understanding of the potential pathogenic and protective functions of TLOs is therefore crucial.

B cells and autoantibodies have long been considered to be the main drivers of autoimmune kidney diseases, such as lupus nephritis[5]. Remarkably, although the presence of lymphocyte clusters dominated by $CD4^-$ T cell populations comprising $CD8^+$ T cells, γδ T cells and double-negative ($CD4^-CD8^-$; DN) T cells[39,40] in the tubulointerstitium is associated with refractory disease and predicts progression to kidney failure in patients with LN, the presence of B cells in these lymphocyte clusters is associated with protection against disease progression[37].

Immune cells, including macrophages and DCs, may enter the glomerulus to instigate damage. Cytotoxic T cells can also enter and cause podocyte apoptosis when the basement membrane is injured[41]. Meanwhile, resident myeloid and infiltrating cells can proliferate locally[6,28].

In models of acute kidney injury (AKI), single-cell transcriptomic analyses of T regulatory cells identified the differential upregulation of regenerative pathways or hyperactive, pro-fibrotic pathways, dependent on environmental cues and stage of injury[42]. These findings suggest that immune cells are subject to plasticity and that their role in the control of damage may change in a temporal manner. Better insights into the pathogenic and regulatory properties of resident and infiltrating immune cells within the kidney parenchyma may reveal opportunities for targeted therapies.

Cytokines and chemokines

Soluble mediators, such as pro-inflammatory cytokines or antibodies, may initiate kidney inflammation by activating resident immune cells to produce various cytokines and chemokines[43]. These mediators are thought to promote the further recruitment of immune infiltrates, resulting in the production of additional cytokines and chemokines and amplification of the local inflammatory response[44]. The pathogenic role of soluble mediators in nephritis is supported by preclinical studies, which have shown that cytokine-blocking treatment suppresses kidney disease. However, the effectiveness of cytokine-blocking therapies in patients is less clear[44].

Unlike cytokines, which are broadly recognized by different types of immune cells, chemokines are selectively used to promote the migration of specific cell populations to specific organs. Thus, some chemokines may exert a direct effect on the kidney through the

recruitment of specific cell populations, with minimal impact on the systemic autoimmune response. Various chemokines – including CCL2, CCL20, CXCL10, CXCL12, CXCL13 and CX3CL1 – are increased in the kidneys of patients with lupus nephritis, with region-specific differences. For example, CXCL13 is highly expressed in the renal cortex, whereas levels of CXCL10 and CXCL12 were significantly increased in both the tubulointerstitial and glomerular regions[45,46]. These findings suggest that chemokines might orchestrate the migration of specific immune cell populations to particular regions of the kidney, and further suggest that targeting of kidney-specific cytokines and/or chemokines may represent a promising strategy for controlling nephritis. However, detailed mechanistic studies are needed to serve as the basis for future drug development.

Insights from single-cell RNA sequencing

The rapid development of single-cell RNA sequencing (scRNA-Seq) technologies has facilitated the detailed characterization of heterogeneous cell populations[47]. The creation of cell atlases[48,49] has confirmed the presence of different immune cells in kidneys under physiological conditions[50]. Notably, these studies identified a unique myeloid population that is distinct from myeloid cells in the blood and a population of $CD4^+$ T cells with an effector memory phenotype[48,49]. To date, scRNA-Seq has provided insights into the complexity of both parenchymal and immune cell landscapes in nephritic kidneys in the context of lupus nephritis, diabetic kidney disease, IgA nephropathy and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis[31,50-55].

Inflammatory macrophages constitute the predominant population of infiltrating immune cells in most chronic kidney diseases (CKDs), and their accumulation is closely associated with the presence of proteinuria and kidney damage[28]. scRNA-Seq studies have identified the presence of resident memory $CD4^+$ T cells and B cells in kidney biopsy samples from patients with lupus nephritis, diabetic kidney disease and IgA nephropathy[50], indicating the existence of shared mechanisms in the development of kidney inflammation across kidney diseases of different aetiologies. The ratio of various immune infiltrates likely varies between diseases and according to disease stage, contributing to the heterogeneous nature of the inflammatory response in individuals with kidney disease. Future scRNA-Seq studies may identify therapeutic targets that are shared between clinical entities and conversely, identify therapeutic targets that are specific to disease aetiology and stage to enable a precision medicine approach to treatment[56,57].

Immune features of kidney parenchymal cells

Although KPCs are traditionally thought to participate in the core functions of the kidney, an emerging body of literature suggests that various KPCs also possess immune regulatory roles. Indeed, KPCs exhibit several characteristic features of immune cells and express components of the innate and adaptive immune cascades that are critical to the inflammatory response in the kidney[58-60] (Fig. 2).

Mesangial cells

Mesangial cells are well known to share numerous molecules with immune cells, particularly with monocytes and macrophages. Moreover, they have a crucial role in preventing the accumulation of aggregated proteins and small immune complexes in the glomerular basement membrane[61] and thereby interact with immune cell processes. Mesangial cell proliferation and the presence of mesangial matrix are consistently observed in kidney tissue of patients with glomerulonephritis[62]. Mesangial cells express Toll-like receptors (TLRs)[62,63], and upon stimulation with appropriate ligands, produce type I IFN[62] – a cytokine that is important in the pathogenesis of SLE[62,64] (Fig. 2).

Available data suggest that the binding of antibodies, including those directed against double-stranded DNA to mesangial cells in the context of lupus nephritis activates an inflammatory signalling cascade that involves mitogen-activated protein kinase and protein kinase C, and ultimately leads to the production of pro-inflammatory cytokines[64,65]. In mouse models of SLE, secretion of IL-6 by mesangial cells acts as an independent driver of glomerulonephritis[66]. Moreover, in patients and mouse models of lupus nephritis, mesangial cells overexpress calcium/calmodulin kinase 4 (CaMK4), a serine/threonine kinase that is necessary for mesangial cell proliferation and IL-6 production (Fig. 2). Interestingly, mesangial cells from lupus-prone MRL/lpr mice that lack CaMK4 do not proliferate in response to platelet-derived growth factor and fail to produce IL-6 (ref. 67). In IgA nephropathy, under-galactosylated IgA1 containing immune complexes activate mesangial cells to produce IL-6 (ref. 68) as well as other cytokines, chemokines and complement[69].

Podocytes and glomerular endothelial cells

Podocytes express MHC class II and CD86, which are required for T cell activation. Mice that lack MHC II specifically in podocytes demonstrate an attenuated response to nephrotoxic serum-induced nephritis[70,71]. The neonatal Fc receptor (FcRn) is expressed in glomerular endothelial cells, podocytes, and proximal tubular epithelial cells (TECs)[72] and has a crucial role in salvaging protein and preventing its loss in the urine. In podocytes cultured in the presence of immune complexes, silencing of FcRn decreased immune complex trafficking to lysosomes and decreased lysosomal surface area and function, suggesting that FcRn-mediated trafficking of immune complexes modulates lysosomal function in podocytes[73].

TLRs have an important role in the development and progression of kidney diseases; their dysregulation is critically involved in various conditions, including urinary tract infections, ischaemia–reperfusion injury, AKI, lupus nephritis and diabetic kidney disease[12]. Both podocytes and renal TECs express TLRs (Fig. 2), which enables them to recognize pathogen-associated molecular patterns and damage-associated molecular patterns. This recognition leads to the induction of chemokines and cytokines involved in the development of glomerular damage, which is achieved through the activation of downstream molecules such as NF-κB, MyD88, IRAK and TRAF6 (refs. 58,74).

In vitro studies have shown that podocytes treated with TNF produce IF-6, which promotes the migration of neutrophils to glomerular endothelial cells[75]. Podocytes also express

TWIST1, a transcription factor that contains a basic helix–loop–helix domain and acts as a common repressor of cell-mediated immunity and cytokine production. In the context of glomerular injury, TWIST1 facilitates the production of CCF2 in glomeruli, which promotes the accumulation and activation of macrophages and exacerbates podocyte injury and proteinuria in mice injected with nephrotoxic serum or the nephrotoxin, adriamycin. However, deletion of *Twist1* in podocytes promoted podocyte injury and proteinuria, suggesting that its upregulation in human and murine models of podocytopathies may represent a compensatory mechanism[76].

Finally, podocytes are not only susceptible to complement-mediated injury but also actively contribute to the production of complement components[77]. Both primary cultured podocytes and immortalized podocytes express a wide range of complement genes under physiological conditions[78]. In addition, exposure of podocytes to puromycin both in vivo and in vitro increases the expression of complement component C3 (ref. 78).

Glomerular endothelial cells may also contribute to the development of nephritis in patients with autoimmune disease. In patients with lupus nephritis, these cells display an IFN signature[79], and produce fractalkine (CX3CL1)[80] as well as other pro-inflammatory cytokines[81].

Tubular epithelial cells

Renal TECs actively contribute to the development of the kidney inflammation by producing pro-inflammatory cytokines and chemokines and by interacting with immune cells[60,82-85]. Renal TECs produce IFNα, which induces – probably in an autocrine manner – a type-I IFN signature that exists only in TECs[86]. Kidney TECs also produce B cell-activating factor (BAFF), a cytokine that is essential for B cell survival and maturation and may help B cells to survive and expand in the kidney[87,88]. TECs also express the receptor for BAFF and it is believed to contribute to the cell atrophy routinely seen in patients with lupus nephritis[60]. Proximal TECs can also produce IL-12p70 and IL-10, through which they control the function of DCs[60,82-85] and B cells[60,82-85], and CX3CR1, which aids the recruitment and retention of myeloid DCs[60,82-85]. Moreover, proximal TECs may contribute to sepsis-induced kidney inflammation and AKI through activation of TLR2–NF-κB–CCL2 signalling[89]. TECs also express the programmed cell death (PD) ligands, PD-L1, and PD-L2 (ref. 85). Activation of the PD-1–PD-L1 signalling in TECs is thought to exert an inhibitory effect on the development of alloreactive T-cell responses[85] (Fig. 2). TECs also produce TGFβ, which induces their senescence and promotes fibroblast proliferation[90].

α-Intercalated cells, traditionally known for their role in acid–base homeostasis, can sense liposaccharide through TLR4 to produce the bacteriostatic protein lipocalin 2 (ref. 91) and the anti-inflammatory cytokine IL-18 (ref. 92) to fend off infections and mitigate inflammation[93]. Information about the numbers and function of these cells in patients with autoimmune kidney disease is not yet available; however, given that urinary tract infections are common in patients with lupus nephritis, we suspect that their function is compromised.

Mesenchymal stromal cells

Mesenchymal stromal cells are multipotent progenitor cells that are present in all tissues; they are immunomodulatory and may exert pro-inflammatory effects in the presence of certain cytokines. Mesenchymal stem cells can be detected in the renal pelvis and the TLOs of lupus-prone mice; following stimulation, they produce a number of pro-inflammatory cytokines and facilitate the formation of TLOs[94].

KPCs undergo a transition to acquire immune cell features during the postnatal period. Studies of single-cell suspensions derived from mature human kidneys and fetal kidneys have revealed that immune cells are spatially distributed throughout the kidney. This spatial distribution enables interaction between epithelial cells and immune cells and is likely important for the instigation of appropriate immune responses. For example, in the context of infection, specific interactions between epithelial cells and immune cells – most notably in the renal pelvis – may orchestrate the localization of antibacterial macrophages and neutrophils to regions of the kidney that are most susceptible. These interactions are mediated through various mechanisms. For example, the expression of TLR4 and its downstream signalling molecule MyD88 in the pelvic epithelium contributes to the localization of immune cells. In addition, epithelial cells of the renal pelvis express CXCL8, which likely promotes the chemotaxis of neutrophils to the region during infection. Notably, the innate immune capability of zonated epithelial cells and the expression of neutrophil-recruiting chemokines in the distal nephron and pelvis are acquired after birth and are not present in fetal kidneys[49].

In addition to the acquisition of immune features during development, KPCs exhibit sex-based transcriptional differences[49]. These differences suggest higher baseline metabolic activity in males and enhanced expression of antioxidant genes in females. Specifically, KPCs from human female kidneys show increased expression of metallothionein genes and genes related to cysteine–glutathione metabolism, which are crucial for cellular antioxidant defence[95]. These findings provide insights into the sexual dimorphism observed for many kidney diseases[96,97].

The immune function of KPCs is also affected by the natural aging process. The impact of cellular senescence and the accumulation of age-modified immune cells in aged kidneys or in kidneys with chronic injury or inflammation has been well-documented[98]. Renal cell senescence is associated not only with the development of AKI and CKD but also with their progression. Notable similarities between senescence and AKI in terms of pathogenic mechanisms, including the secretion of pro-inflammatory and pro-fibrotic factors, the presence of oxidative stress, mitochondrial dysfunction and loss of renoprotective factors[99]. Aged kidneys develop TLOs following AKI, likely because of maladaptive repair, and their presence is associated with the severity of kidney injury in both mice and humans[100]. Notably, in aged kidneys after ischaemia–reperfusion injury, the development of the age-dependent lymphocyte subpopulations, $CD153^{+}PD\text{-}1^{+}CD4^{+}$ senescence-associated T (SAT) cells and $CD30^{+}T\text{-}bet^{+}$ age-associated B cells (ABCs) is spatiotemporally synchronized within TLOs[100]. This synchronized development is mediated through the CD153–CD30 signalling pathway as evidenced by the finding that transplantation of bone marrow from CD153-deficient mice into aged $Rag2^{-/-}$ mice after ischaemia–reperfusion injury attenuates

TLO formation[100]. SAT cells in the kidney and ABCs in the spleen have shared T cell and B cell receptor sequences, respectively, suggesting the possible circulation of SAT cells and ABCs between the spleen and kidney.

Kidney draining lymph nodes

Lymph nodes are the main sites at which cells of the adaptive immune system are modified and activated to ensure specificity of the immune response. From the kidney, lymphatic vessels carry soluble antigens and cells to kidney-draining lymph nodes (KLNs) (Fig. 3). Under physiological conditions, DCs in the KLN handle kidney-filtered antigen and establish immune tolerance by upregulating PD-L1 (ref. 101). DCs also traffic from the kidney to the KLN[102], where they might participate in establishing tolerance.

Mesenchymal stromal cells that reside within lymph nodes are called FRCs. These cells perform a multitude of vital activities to maintain the proper functioning of the lymph node, including the deposition of extracellular matrix, support of blood vessels, facilitation of interactions between antigen-presenting cells and T cells, and promotion of lymphocyte survival[103-108]. A series of experiments demonstrated the importance of KLN FRCs in directing the immune response to a variety of kidney injuries. For example, in response to ischaemia-perfusion injury of the kidney, FRCs in the KLN of mice produce extracellular matrix fibres such as fibronectin. These fibres provide structural support for the proliferation and expansion of HEVs, which are lymph node-restricted segments of vasculature through which circulating naïve T cells enter from the blood[108] (Fig. 3). Ablation of FRCs via administration of diphtheria toxin in transgenic *Ccl19*^{Cre} × iDTR mice abrogated the expansion of HEVs and the activation of IFN-γ-producing CD4^{+} T cells in the KLN[108]. These changes were associated with a reduction in kidney damage following ischaemia–reperfusion injury[108]. Similar microarchitectural changes occurred in the KLNs of mice after the injection of nephrotoxic serum[106]. Similar to observations following ischaemia–reperfusion injury, ablation of FRCs in the KLN in *Ccl19*^{Cre} × iDTR mice also ameliorated kidney injury following the injection of nephrotoxic serum[106] or after unilateral ureteral obstruction[107].

Of note, the phenotype of KLN FRCs changes with progression of kidney injury, such that at the end of the acute phase of the immune response to ischaemia–reperfusion injury, the FRCs support a more immunoregulatory response that dampens inflammation and promotes repair[108]. Use of a blocking antibody to lymphotoxin-β receptor (LTβR), a cardinal membrane protein expressed by FRCs that dictates their activity, before and after bilateral ischaemia–reperfusion injury, increased fibrogenic activity in the KLN and exacerbated kidney damage[108]. Together, these studies highlight the importance KLN FRCs in balancing the pro-inflammatory and regulatory immune responses in the kidney following kidney injury. The role of KLNs in shaping kidney inflammation in lupus nephritis and other autoimmune disorders remains unclear but is a topic of interest, given the role of KLNs in establishing immune tolerance to antigens and autoantigens produced in the kidney.

Cell crosstalk

Immune cells that infiltrate the kidney produce cytokines that orchestrate the phenotype and function of both resident immune cells and KPCs in nephritic kidneys[43] (Fig. 4). Concomitantly, KPCs have the ability to sense pro-inflammatory signals, adopt immune functions and influence immune cells[43]. These interactions require engagement between cytokines and chemokines with receptors on KPCs to establish cross-communication between kidney-resident cells and immune cells[109]. Evidence from preclinical studies indicates that targeting of interactions between KPCs and immune cells in the kidney may be a promising strategy to attenuate renal inflammation in various forms of nephritis[4,110].

Lupus nephritis

TECs, mesangial cells and podocytes are injured in lupus nephritis, demonstrating alterations in their cellular metabolism and increased susceptibility to cell death[4,39,111,112]. These changes, along with aggravation of hypoxia, establish a pro-inflammatory microenvironment to which infiltrating immune cells must adapt[37,113]. For example, under physiological conditions, TECs maintain an immunosuppressive environment by limiting the local availability of metabolites, such as arginine[4]. Stimulation with IL-23 leads to the loss of this immunosuppressive ability and the increased availability of arginine for infiltrating immune cells[4] resulting in the acquisition of a pro-inflammatory phenotype, characterized by the production of pro-inflammatory cytokines and chemokines[114]. Levels of IL-23 are, accordingly, elevated in the sera of patients with LN[115] and probably also in the sera of patients with other types of glomerulonephritis.

Enhanced ferroptosis has been observed in TECs of biopsy samples from patients with lupus nephritis[111]. This type of cell death may be more immunogenic than other forms of necrosis by accelerating the release of self-antigens to promote and sustain local inflammation[25,116]. Mesangial cells and podocytes can also present antigens and produce pro-inflammatory cytokines and chemokines in the context of lupus nephritis[117-119]. The application of multiplexed confocal microscopy to kidney samples from patients with lupus nephritis has revealed the presence of immune cell clusters involving different types of lymphocytes in different regions of the kidney[37]. Notably, B cells, often along with $CD4^+$ T cells, are organized into large cell clusters and reside in the periglomerular area, whereas $CD4^-$ T cells are always found in the interstitium within relatively small cell clusters[37]. This observation suggests the existence of diverse microenvironment settings in different areas of inflamed kidneys, potentially contributing to distinct types of inflammatory responses.

Acute kidney injury

AKI is a common clinical entity that is characterized by injury, predominantly of proximal TECs[120]. In an ideal scenario, the injured tissue undergoes self-repair mechanisms in a process that involves the activation of reparative macrophages to clear cell debris and the proliferation of surviving tubular cells, resulting in the restoration of the nephron structure[121]. However, failed tubule repair in the early phase of AKI can trigger a second wave of inflammation characterized by the persistent accumulation of macrophages and increased influx of neutrophils and T cells to the kidneys, which facilitate the transition from

AKI to CKD[122-124]. This perpetuating process indicates the presence of intricate crosstalk between proximal TECs and various immune cell populations. Moreover, the heightened expression of T cell immunoglobulin and ITIM domain (TIGIT) on kidney infiltrating T cells, which has been observed in AKI[125], might contribute to the adaptive response to the local microenvironment by altering intrinsic T cell metabolism. It would be of interest to investigate which kidney-resident cells engage with infiltrating T cells by expressing the TIGIT ligands CD155 (PVR) and CD112 (PVRL2).

Kidney allograft rejection

Kidney allograft rejection initiates when a donor-derived alloantigen induces an immune response against the graft; TECs are one of the main targets of inflammatory insults during this process. Kidney epithelial cells display all the factors necessary to activate $CD4^+$ T cells, such as HLA-DR, CD80 and adhesion molecules[126,127]. The infiltration of different types of immune cells, especially T cells and macrophages, into the interstitium is observed in rejected grafts. DCs, NK cells, B cells and plasma cells are also present albeit in lower numbers[128]. Interestingly, interstitial inflammation is more frequent and severe in the cortex than in the medulla, suggesting the presence of distinct immune environments within different renal compartments[129]. This observation is further supported by the finding that DCs in the medulla are less well equipped than bone marrow-derived DCs to process and present antigen[130]. In contrast to acute rejection, wherein immune infiltrates are distributed throughout the entire kidney, chronic rejection is characterized by the formation of organized TLOs[131,132]. Notably, these TLOs can be identified within the grafts before the lesions develop, although studies that have examined the correlation between the formation of intrarenal TLOs and chronic rejection have reached conflicting conclusions[133]. Crosstalk between KPCs and immune infiltrates in different regions of the kidney, which are characterized by distinct physicochemical microenvironments, may be diverse and the processes leading to the formation of TLOs distinctly different. However, it remains unclear whether these TLOs possess pathogenic or regulatory capacity.

ANCA-associated vasculitis

Small vessels in the kidney, including capillaries, venules and arterioles are the main targets of immune cell infiltrates in ANCA-associated vasculitis. Proteinase 3 is one of the antigens recognized by ANCA and is expressed by neutrophils. Moreover, evidence from experimental models suggests that resident $CD4^+$ T cells, especially Th17 cells, can promote the progression of ANCA-associated glomerulonephritis through the production of IL-17 (ref. 54). As described earlier, TECs can produce chemokines in response to inflammatory cytokines[4,110], and may therefore participate in cellular crosstalk in inflamed kidneys to exacerbate glomerulonephritis progression. Insights into such crosstalk may facilitate the development of targeted therapies for patients with vasculitis.

Targeting KPCs to treat glomerulonephritis

Mainstay treatment strategies for patients with immune-mediated diseases include classic immunosuppressive drugs, such as prednisone and cyclophosphamide, and biologics, which interfere with the function of immune cells. Precision medicine calls for the delivery of the

right drug, to the right patient, at the right time. However, the idea that a precision medicine approach could be applied to specific cells or organs to avert or mitigate injury has been insufficiently explored.

We previously established that the Ser/Thr kinase, CaMK4, which is expressed in T cells in patients with SLE, increases the production of pro-inflammatory IL-17 and decreases the production of immunoregulatory IL-2 through distinct epigenetic modulation of the two gene loci[134,135]. Genetic, or small molecule inhibition of CaMK4 suppressed autoimmunity and nephritis in lupus-prone mice[3,4,134]. More importantly, cell-targeted delivery of a CaMK4 inhibitor to $CD4^+$ T cells, suppressed autoimmunity and nephritis in lupus-prone mice[136]. Based on the finding that podocytes from lupus-prone mice and patients with lupus nephritis express increased amounts of CaMK4, and that CaMK4 can suppress the expression of nephrin and enable the destruction of synaptopodin, thereby compromising podocyte structure[3,137], we attempted podocyte-specific delivery of a CaMK4 inhibitor in MRL/*lpr* lupus-prone mice using nanoparticles loaded with a small drug inhibitor and tagged with nephrin or podocin antibodies. Indeed, such cell-specific treatment averted the development of lupus nephritis, including the deposition of immune complexes. Interestingly, humoral and cellular elements of the systemic autoimmune response remained intact[3], suggesting that the glomerular deposition of immune deposits may only occur under conditions of compromised podocyte function.

We subsequently found that TECs from MRl/*lpr* lupus-prone mice also expressed increased amounts of CaMK4. Administration of nanoparticles loaded with a CaMK4 inhibitor targeted to TECs mitigated proteinuria and interstitial inflammation, again, without affecting systemic autoimmunity[4]. This observation suggests that TECs may behave as pro-inflammatory cells in lupus nephritis by attracting immune inflammatory cells and that suppression of CaMK4 mitigates this activity. As discussed above, TECs lose their immunosuppressive phenotype following stimulation with IL-23 (ref. 4). Specifically, binding of IL-23 to the IL-23 receptor expressed on the surface of TECs upregulates CaMK4 expression and alters their metabolic profile, which may enable the accumulation of immune cells[4].

As described earlier, HEVs are specialized segments of the vasculature that are unique to secondary lymphoid organs, such as the lymph nodes and tonsils[138]. They are the gateways through which naïve T cells enter these organs, and they possess a family of membrane glycoproteins called peripheral node addressin (PNAd), which are the receptors for L-selectin, a surface protein expressed by naïve T cells[138]. Also, as described earlier, KLNs are the main sites for modulation of the adaptive immune response to renal damage following common types of kidney injury, such as ischaemia–reperfusion injury and glomerulonephritis[106-108]. Therefore, HEVs represent an attractive target for precision therapies directed at manipulating the local immune response in the context of kidney injury.

Targeted nanoparticles have already been created to target HEVs; future studies could use these carriers to deliver therapeutics to KLNs. In a mouse model of heart transplantation, delivery of a PNAd-binding IgM antibody, MECA-79, conjugated to a polymeric nanoparticle and loaded with the immunoregulatory molecule anti-CD3 – a nanoparticle

that localized to activated allograft-draining lymph nodes – increased the population of T regulatory cells within draining lymph nodes and improved allograft survival[139]. Another antibody, MHA112, binds to PNAd with greater affinity than MECA-79; antibody–drug conjugates comprising MHA112 and the anticancer drug paclitaxel successfully targeted HEVs in tumour-draining lymph nodes, reducing tumour size and metastatic lesions[140].

These preliminary successes provide proof of concept that a targeted, precision medicine approach could be used in the treatment of immune-mediated kidney diseases, either through the delivery of a targeted therapeutic to the specific cell or organ that undergoes injury or participates in perpetuation of the injurious response, or to local lymph nodes to modulate immune and autoimmune responses.

Remaining questions and future directions

There is no doubt that inflammation in the kidney occurs after immune tolerance has been lost in the periphery, or in response to an alloantigen or to kidney injury. However, it is increasingly apparent that kidney-resident cells themselves have an active role in modulating and propagating the inflammatory response. Better understanding of these novel concepts is needed as we strive to treat individuals with kidney inflammation more effectively.

As described earlier, KPCs express molecules that are shared with immune cells and the expression of these molecules is modulated during inflammation. For example, TECs or podocytes express receptors for IL-23. Activation of these receptors by circulating IL-23 can initiate a signalling process that alters their metabolism and the distribution of metabolites in the surrounding milieu. As mentioned above, IL-23 inhibits the ability of TECs to degrade arginine, which increases its availability as a fuel to infiltrating immune cells[4]. Technological advances should improve our understanding of the metabolic alterations that occur in the interstitium and pericellular space of the injured kidney and provide insights into how metabolites may alter the function of infiltrating immune cells[141].

Podocytes, in response to aberrantly glycosylated IgG, upregulate the expression of costimulatory molecules along with major histocompatibility antigens. From an immunology point of view, podocytes exposed to autoantibodies or other inflammatory signals, may function as bona fide antigen-presenting cells and thereby inform and modulate passing lymphocytes. Whether kidney-infiltrating lymphocytes at this point have already differentiated into pro-inflammatory cells in the spleen or other secondary lymphoid organs, or if they are stimulated and become pathogenic after they enter the kidney, is unclear. We also do not know the spectrotype of the T cell receptors of infiltrating cells beyond the fact that they are limited[4]. Moreover, the nature of the autoantigen or antigen that they recognize is still unknown. However, we know that the kidney environment promotes a pro-inflammatory milieu for the invading T cells. Increased hypoxia in the context of LN promotes the differentiation of Th17 cells through activation of HI1α[39]; high levels of sodium in the interstitial space may also contribute to the generation of such cells[142,143]. A hypothesis to be further tested is that T cells are presented with antigen in situ and the unique kidney environment enables their differentiation into pro-inflammatory cells.

The clinical relevance of the formation of TLOs by infiltrating immune cells has been established, and the formation of such structures are predictors of poor kidney function[37]. However, the sequence of events leading to their formation is still unknown. HEVs are of structural and functional importance in the formation of secondary lymphoid organs, and we can predict that their appearance would facilitate the formation of TLOs in the kidney. However, we do not know what drives the appearance of HEVs in the kidney. We also do not know whether TLOs that form in the renal pelvis or cortex area differ in their cell composition and clinical importance. TECs in the renal pelvis upregulate molecules that facilitate the entry of neutrophils[60], which has teleological value given the susceptibility of this region to infections. However, in-depth characterization of infiltrating lymphocytes in the context of inflammatory disease is needed. Beyond the fact that some of these cells produce IL-17 (ref. 144), our understanding is fairly limited.

The presence of B cells in the kidney tissue of patients with lupus nephritis has been proposed to protect against kidney failure[37], which is counterintuitive given the importance of B cells in the pathogenesis of autoimmunity. However, these cells may be regulatory in nature or produce protective cytokines[24]. We do not know whether regulatory T cells are present, whether they can be expanded within the kidney tissue[145] or whether they can be bestowed with tissue repair capabilities[146,147]. Last, we do not know how lymphocytes situated adjacent to KPCs influence their transcriptomic profile through cognate interactions. The application of new technologies, such as high-resolution spatial imaging should provide detailed insights into the interactions between resident and infiltrating cells.

An interesting concept is that in the setting of a systemic autoimmune disease, the kidney is not injured unless certain biochemical or metabolic processes are set in motion. This concept reflects clinical experience wherein not all individuals with systemic autoimmunity develop nephritis[14]. Our own studies have shown that podocytes, TECs and mesangial cells suffer injury only when they can upregulate CaMK4. These findings imply that if a patient with SLE cannot upregulate CaMK4 because of genetic, epigenetic, hormonal or other reasons, then they will not develop nephritis. Obviously, other molecules besides CaMK4 are likely involved in the injury of KPCs, and their regulation will likely be of comparable importance. This line of reasoning supports a therapeutic approach that enables the modulation of molecules that are specific to kidney-resident cells, including KPCs and kidney-resident immune cells. The discovery of additional pathways that are involved in the injury of KPCs in the setting of systemic autoimmunity or other inflammatory processes will enrich our understanding of mechanistic pathways and identify new approaches to treating patients with immune-mediated or inflammatory kidney diseases.

Conclusions

Inflammation in the kidney occurs after loss of immune tolerance in the periphery, or in response to an alloantigen or kidney injury, and can lead to the development of CKD and kidney failure. The inflammatory response may involve the deposition of antibody, complement and the infiltration of cells of the innate and adaptive immune systems. These infiltrating cells may expand their pro-inflammatory capacity in the hypoxic and hyperosmotic kidney interstitium, although some infiltrating cells might possess

regulatory activity. KPCs can express molecules that classically belong to cells of the immune system. Such molecules most probably facilitate crosstalk between infiltrating immune and parenchymal cells. Available evidence suggests that immune cells can alter the transcriptional profile of KPCs, promoting the expression of immune molecules. Conversely, KPCs can attract and retain inflammatory cells. Upregulation of specific signalling molecules, such as CaMK4, by KPCs may be needed for cell and organ injury to occur; hence, targeted inhibition of these molecules may open up new precision medicine approaches to the treatment of kidney inflammation and disease. KLNs seem to be important for the development of kidney inflammation as they represent the site in which tolerance to kidney-derived autoantigens is developed. Targeting the immune response in the KLNs should offer additional therapeutic options.

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Key points

- Non-myeloid kidney parenchymal cells (KPCs) express molecules that are shared with immune cells; the expression of these molecules may have distinct topological associations and may increase in response to inflammation.
- Kidney injury can induce the infiltration of immune cells; these cells may have protective or pro-inflammatory features depending on the phase of the disease process. In addition, kidney-resident immune cells may have a surveillance or regulatory role in the kidney but can accumulate in response to injury.
- Components of the immune system, such as autoantibodies, cytokines and immune cells, can influence the metabolic profile of KPCs in the kidney.
- Conversely, KPCs can contribute to inflammation by providing metabolites or through the secretion of chemokines and cytokines.
- The cortex and the medulla of kidney tissue can contain distinct types of tertiary lymphoid organs, which may possess pathogenic or regulatory properties.
- Targeted delivery of drugs to KPCs holds promise for preventing or reversing the inflammatory response in specific forms of kidney injury and disease.

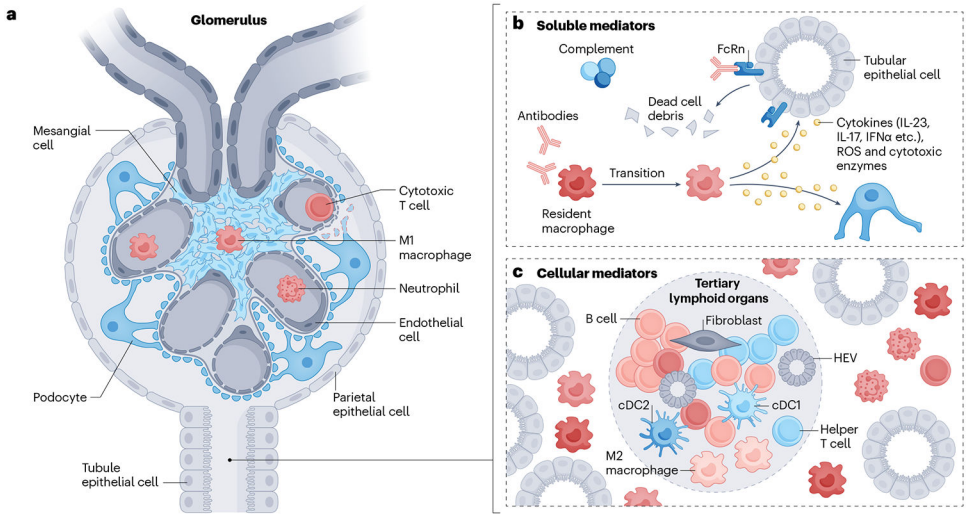

Fig. 1 |. Soluble and cellular mediators of inflammation in the kidney.

a, immune cells, including macrophages and dendritic cells, may enter the glomerulus to instigate damage; cytotoxic T cells might also enter and cause podocyte apoptosis when the basement membrane is injured. **b**, Activated components of the complement system and/or autoantibodies can attack kidney parenchymal cells (KPCs), such as tubular epithelial cells, directly, to cause tissue damage. Alternatively, they can recruit and/or activate myeloid cells to induce the release of cytokines, reactive oxygen species (ROS) and cytotoxic enzymes. **c**, Different immune cell clusters composed of different types of lymphocytes can be observed in the interstitial region. Some clusters display features typical of secondary lymphoid organs, including the presence of T cell and B cell zones aligned with the formation of high endothelial venules (HEVs) and new lymphatic vessels; these clusters are termed tertiary lymphoid organs.

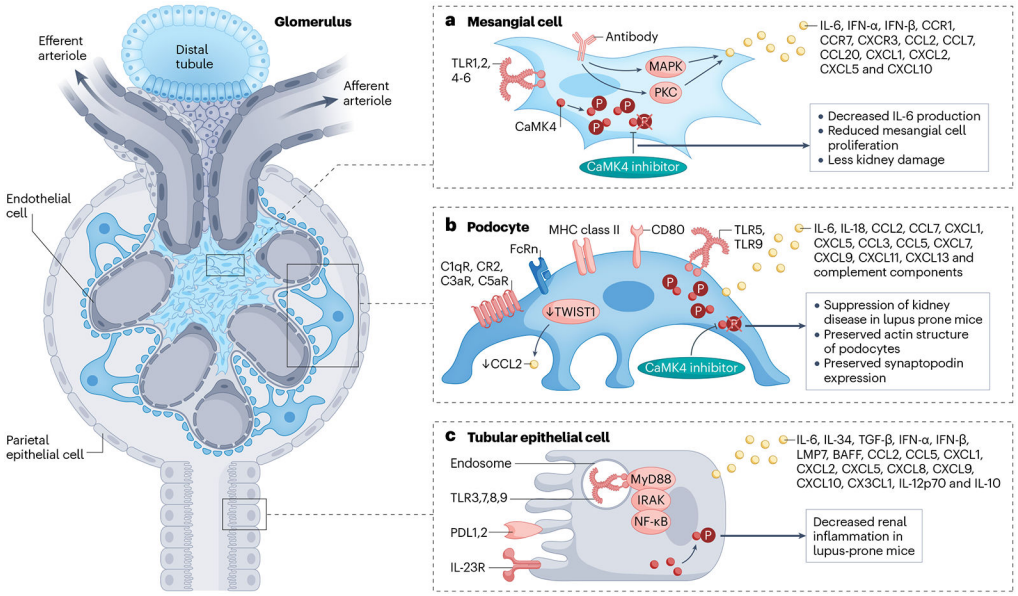

Fig. 2 |. Immune features of kidney parenchymal cells.

Kidney parenchymal cells, including podocytes, tubular epithelial cells and mesangial cells, express molecules that are typical of the innate and adaptive immune systems. These molecules have important roles in the recruitment of immune cells and in the development of inflammatory responses. **a**, Mesangial cells have long been known to express cytokines and chemokines in response to circulating inflammatory signals. For example, IL-6 can independently cause mesangial proliferation. Signalling molecules, such as CaMK4, may control the production of cytokines, and may therefore represent a treatment target. **b**, Podocytes produce and express molecules typically produced by cells of the immune system, including HLA, costimulatory molecules, the neonatal Fc receptor (FcRn), TLRs, and chemokines and their receptors, along with complement components and receptors. The transcription factor TWIST1 may suppress the production of CCL2 in healthy glomeruli. Podocyte injury may lead to the altered expression of molecules such as CaMK4, which can directly compromise the expression of molecules involved in their function (e.g. nephrin) or structure (e.g. synaptopodin). **c**, Similarly, TECs may produce cytokines and chemokines and their receptors, which may promote the recruitment of inflammatory cells. Such cells may, through the further production of cytokines, contribute to the damage of TECs. Again, alterations in the expression of molecules such as CaMK4 may contribute to the accumulation of immune cells and may therefore representa therapeutic target. FcRn, neonatal Fc receptor; TLR, Toll-like receptor; PDL1, programmed death ligand 1; IRAK, IL-1 receptor-associated kinase; TRAF6, TNF receptor-associated factor 6; BAFF, B cell–activating factor; LMP7, low–molecular mass polypeptide-7; CAMK4, calcium/calmodulin dependent protein kinase IV.

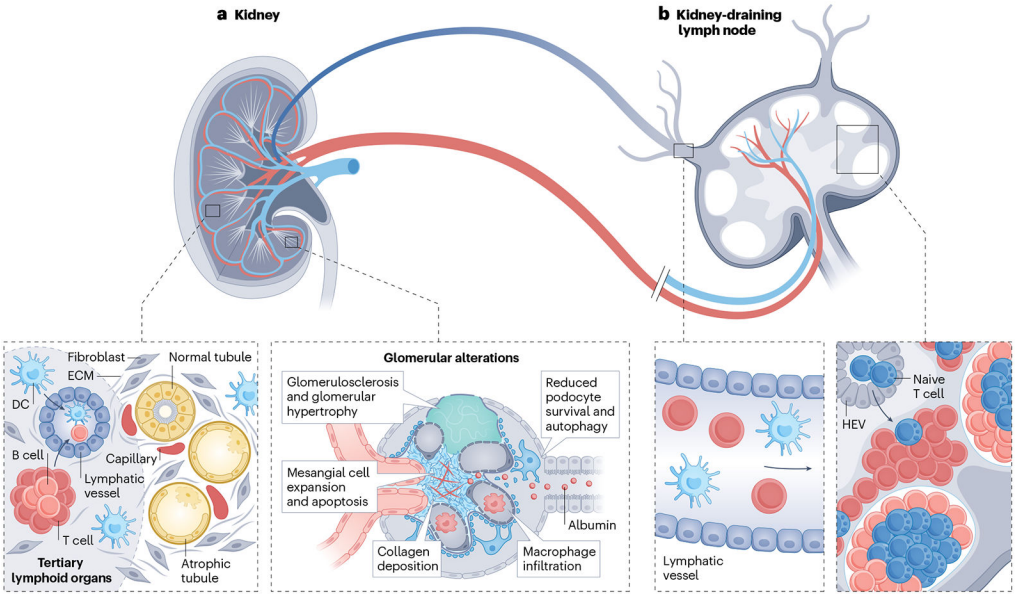

Fig. 3 | Lymphoid organs in kidney disease.

a, Aged and chronically diseased kidneys can contain atrophic tubules, sclerotic glomeruli, and fibrosis, as well as tertiary lymphoid organs, which are lymphoid aggregates of T cells and B cells, high endothelial venules (HEVs) and lymphatic vessels. **b**, Kidney-resident dendritic cells (DCs) and T cells can circulate via lymphatic vessels from the kidney cortex to the kidney-draining lymph node (KLN), where they interact with T cells in the paracortex with the assistance of fibroblastic reticular cells. The fibroblastic reticular cells produce conduits composed of extracellular matrix (ECM), which provide structural support for the proliferation and expansion of HEVs, through which naïve T cells enter the KLN from the systemic circulation. Activation of T cells in the KLN is critical to the pathogenesis of glomerulonephritis, ischaemia–reperfusion injury and unilateral ureteral obstruction in mice.

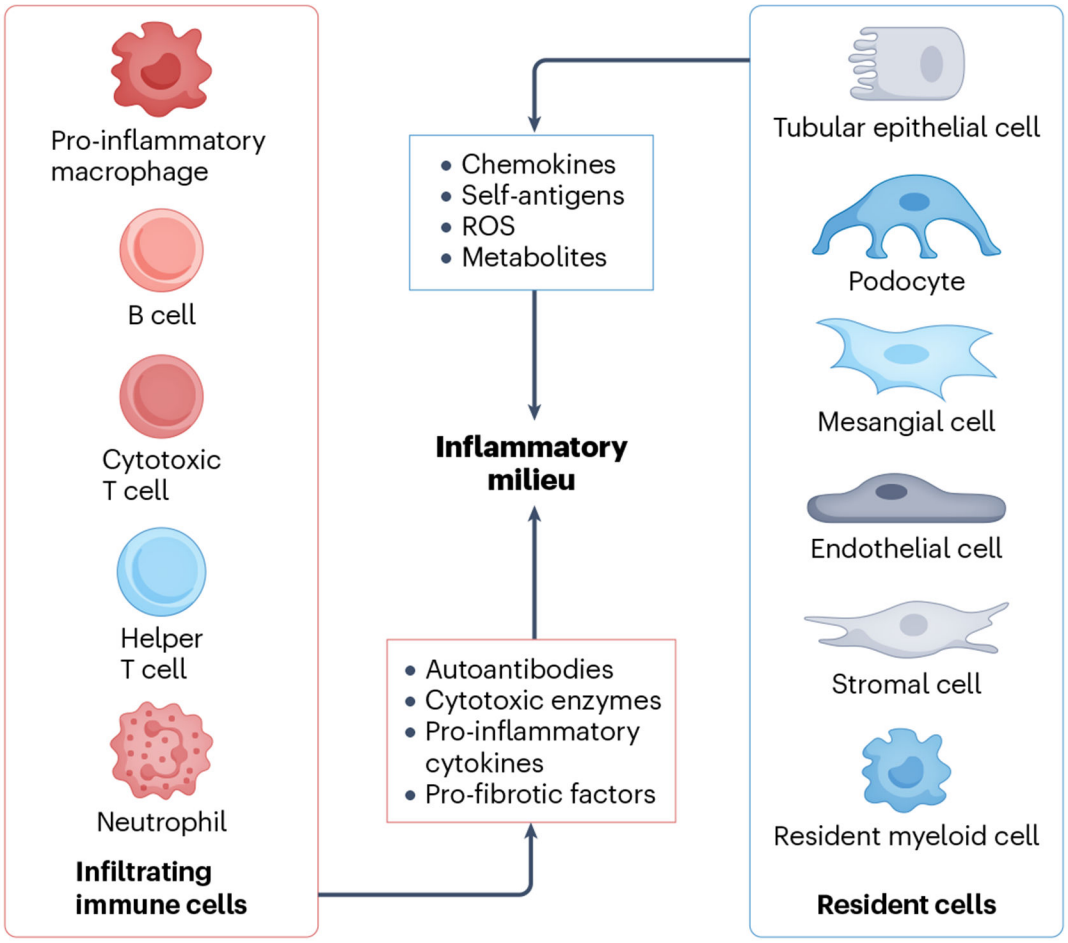

Fig. 4 |. Intercellular crosstalk within the kidneys between resident and infiltrating cells. Immune cells attack tissue resident cells by producing various pathogenic factors such as antibodies, pro-inflammatory cytokines, pro-fibrotic factors and cytotoxic enzymes. Conversely, injured tissue resident cells, including resident immune cells and kidney parenchymal cells, respond by altering the local inflammatory milieu, which contributes further to the progression of renal inflammation. ROS, reactive oxygen species.