The immune system and kidney disease: basic concepts and clinical implications

Christian Kurts[1], Ulf Panzer[2], Hans-Joachim Anders[3] and Andrew J. Rees[4]

Abstract | The kidneys are frequently targeted by pathogenic immune responses against renal autoantigens or by local manifestations of systemic autoimmunity. Recent studies in rodent models and humans have uncovered several underlying mechanisms that can be used to explain the previously enigmatic immunopathology of many kidney diseases. These mechanisms include kidney-specific damage-associated molecular patterns that cause sterile inflammation, the crosstalk between renal dendritic cells and T cells, the development of kidney-targeting autoantibodies and molecular mimicry with microbial pathogens. Conversely, kidney failure affects general immunity, causing intestinal barrier dysfunction, systemic inflammation and immunodeficiency that contribute to the morbidity and mortality of patients with kidney disease. In this Review, we summarize the recent findings regarding the interactions between the kidneys and the immune system.

[1]*Institutes of Molecular Medicine and Experimental Immunology (IMMEI), Rheinische Friedrich-Wilhelms-Universität, Sigmund-Freud-Str. 25, 53105 Bonn, Germany.*
[2]*III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.*
[3]*Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians Universität München, Ziemssenstr. 1, 80336 München, Germany.*
[4]*Clinical Institute of Pathology, Medical University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria.*
e-mails: ckurts@web.de; panzer@uke.de; hjanders@med.uni-muenchen.de; andrew.rees@meduniwien.ac.at
All authors contributed equally to this work.
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Considerable progress has been made both in understanding the basic immune mechanisms of kidney disease and in translating these findings to clinical therapies. Sophisticated animal studies combined with the analysis of clinical samples have led to a precise knowledge of the autoimmune targets and of the mechanisms responsible for kidney injury. Kidney diseases are highly prevalent and cost-intensive, but many discoveries in renal immunology are not widely known in the immunological community, although they are often relevant to diseases that affect other organs.

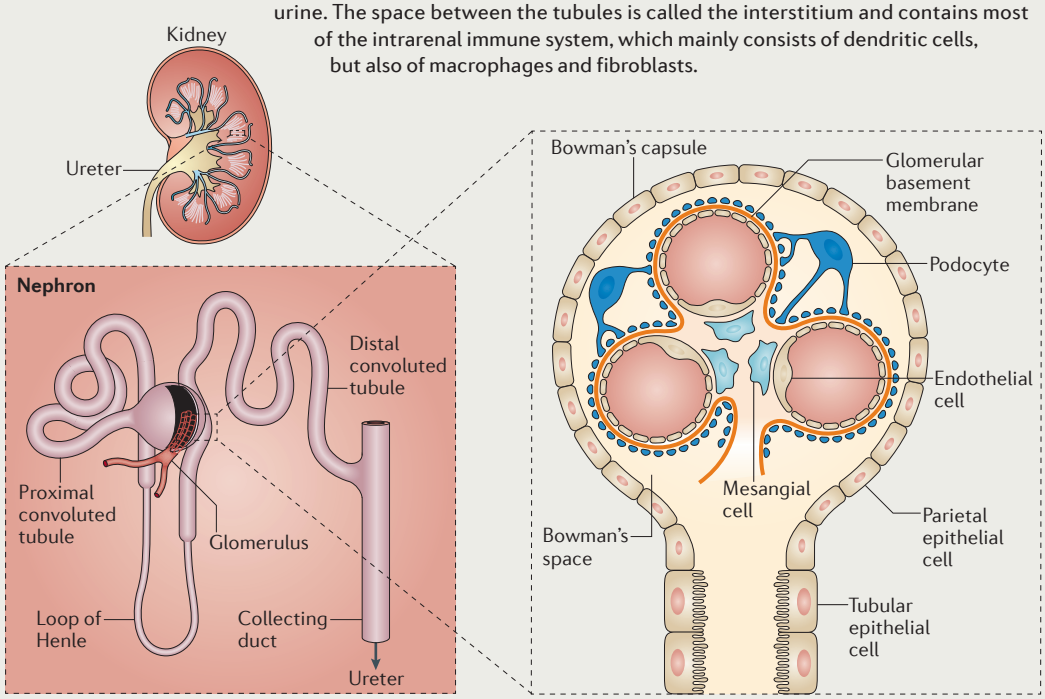
In this Review, we discuss recent advances in our understanding of immune-mediated kidney diseases, emphasizing those of particular relevance to the wider immunology community and those that have led to a better understanding of basic immunological mechanisms. We have had to be selective in the topics considered and so have excluded a discussion of acute kidney injury, kidney transplantation and alloimmunity, as well as of systemic diseases with associated kidney disease, such as type 2 diabetes and hypertension, that are not primarily caused by the immune system, despite the involvement of innate (and possibly adaptive) immune responses in the renal injury they cause. Here, we discuss the innate immune mechanisms of kidney injury and introduce novel concepts about the role of the cellular immune responses that drive renal disease. Moreover, we summarize recent discoveries about complement- and antibody-mediated nephritis, and we discuss kidney pathologies that are mediated by renal autoantigen-specific antibodies, especially those that are induced by crossreactive microorganism-specific antibodies. Finally, we describe how the disruption of kidney function and kidney pathologies can influence systemic immune responses.

Kidney-resident immune cells

In the kidneys, toxic waste products of metabolism are removed from the blood by nephrons. Each nephron contains one glomerulus, which functions as a size-selective filter that retains molecules above ~50 kDa in the blood. Compounds of lower molecular mass pass through the glomerular filter, enter the tubular system and are excreted with the urine unless they are reabsorbed by the tubular epithelium (BOX 1). The kidneys produce several hormones that directly or indirectly affect immune responses, including vitamin D, which regulates bone homeostasis and phagocyte function, erythropoietin, which is induced in response to hypoxia to regulate erythropoiesis, and renin, which induces angiotensin and aldosterone to regulate electrolyte balance, extracellular osmolarity and blood pressure.

Box 1 | **Basic kidney anatomy and physiology**

The kidneys purify toxic metabolic waste products from the blood in several hundred thousand functionally independent units called nephrons. A nephron consists of one glomerulus and one double hairpin-shaped tubule that drains the filtrate into the renal pelvis. The glomeruli located in the kidney cortex are bordered by the Bowman's capsule. They are lined with parietal epithelial cells and contain the mesangium with many capillaries to filter the blood. The glomerular filtration barrier consists of endothelial cells, the glomerular basement membrane and visceral epithelial cells (also known as podocytes). All molecules below the molecular size of albumin (that is, 68 kDa) pass the filter and enter the tubule, which consists of the proximal convoluted tubule, the loop of Henle and the distal convoluted tubule. An intricate countercurrent system forms a high osmotic gradient in the renal medulla that concentrates the filtrate. The tubular epithelial cells reabsorb water, small proteins, amino acids, carbohydrates and electrolytes, thereby regulating plasma osmolality, extracellular volume, blood pressure and acid–base and electrolyte balance. Non-reabsorbed compounds pass from the tubular system into the collecting ducts to form urine. The space between the tubules is called the interstitium and contains most of the intrarenal immune system, which mainly consists of dendritic cells, but also of macrophages and fibroblasts.



Nephrons
Anatomically and functionally independent kidney units that each consist of one glomerulus and one tubule. The nephron delivers urine into collecting ducts that empty into the renal pelvis and, through the ureters, into the urinary bladder.

Glomerulus
An anatomical structure that is located in the kidney cortex and that filters blood into the tubular system.

Tubulointerstitium
The space between the tubuli and glomeruli, which contains capillaries, fibroblasts and dendritic cells, and thus is an important site for the progression of nephritis.

Bacterial pyelonephritis
A bacterial infection of the kidney, mostly due to uropathogenic *Escherichia coli* that ascend through the urethra, bladder and ureter into the kidneys.

Under homeostatic conditions, the resident immune cells of the kidneys include dendritic cells (DCs) and macrophages, as well as a few lymphocytes[1–4]. DCs are restricted to the tubulointerstitium and are absent from the glomeruli[1,2]. In mice, kidney DCs are $CD11c^+CD11b^+F4/80^+CX_3CR1^+CD8^-CD205^-$ and have a transcriptome that is typical of DCs resident in various non-lymphoid tissues[5,6]. Kidney DCs are derived from monocytes and from common DC precursors (CDPs), but in contrast with other organs, some CDP-derived kidney DCs express CD64 (also known as FcγRI)[7]. Kidney DCs function as sentinels in homeostasis, local injury and infection[3,8]. They rapidly produce neutrophil-recruiting chemokines during bacterial pyelonephritis, which is the most prevalent kidney infection[8]. Neutrophils can also be recruited by tubular epithelial cells, but not as quickly as by DCs. Mice lacking expression of CX_3C-chemokine receptor 1 (CX_3CR1) have a selective reduction in kidney DC numbers[9]. There is also a high renal expression of its ligand CX_3C-chemokine ligand 1 (CX_3CL1)[10], which suggests that the CX_3CR1–CX_3CL1 chemokine pair are important for DC recruitment to the kidney and that CX_3CR1 might be a specific therapeutic target to modulate DC numbers in the kidneys. In renal ischaemia (which is relevant in kidney transplantation) and in ureteral obstruction, renal DCs promote tissue injury by producing pro-inflammatory cytokines[11,12]. Basic leucine zipper transcriptional factor ATF-like 3 (BATF3)-dependent $CD103^+$ tissue DCs, which can cross-present antigens to $CD8^+$ T cells, are rare and their function in the kidney is unclear[13]. Macrophages are preferentially found in the renal medulla and capsule[1] and have homeostatic and repair functions[14]. There are also mast cells in the kidney tubulointerstitium but their function is poorly understood[15–17]. In addition, the role of innate-like lymphocytes is currently unclear. Finally, the renal lymph nodes represent a priming site for nephritogenic T cells during renal inflammation[18,19].

Low-molecular-mass proteins can pass through the glomerular filter but are reabsorbed and degraded by tubular epithelial cells. However, some of these proteins are captured by renal DCs or reach the renal lymph nodes by lymphatic drainage within seconds after filtration[20]. Importantly, filtered proteins are concentrated in

Box 2 | **Kidney disorders grouped by their involvement in immunity**

Kidney disorders that are initiated and mainly mediated by an immune response

- Renal infections with renotrophic pathogens, including uropathogenic *Escherichia coli* (UPEC), Hantan virus, BK virus, *Leptospira* spp., *Mycobacterium tuberculosis* and HIV
- Extrarenal infections with renal manifestations, including septic kidney injury, immune complex-mediated nephritis (for example, post-infectious glomerulonephritis and endocarditis, hepatitis and virus-related immune complex glomerulonephritis), interstitial nephritis and HIV nephropathy
- Systemic autoimmunity against ubiquitous antigens with renal inflammation, including IgA nephropathy or Henoch–Schönlein purpura, lupus nephritis, Sjögren's syndrome, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, interstitial nephritis, secondary membranous nephropathy and antibody-mediated forms of atypical haemolytic uraemic syndrome (aHUS)
- Immune responses against renal antigens, including anti-glomerular basement membrane (anti-GBM) autoimmune disease, the autoimmune disease primary membranous nephropathy and allograft rejection
- Other systemic disorders that affect the kidneys and that have genetic (including, complement C3 glomerulonephritis and aHUS) or unclear (including, minimal change disease and renal sarcoidosis) causes

Kidney disorders that involve renal inflammation as a secondary mechanism

- Systemic autoimmunity against ubiquitous antigens with renal manifestations causing renal vascular obstruction and ischaemia, including scleroderma renal crisis, panarteritis nodosa, giant cell vasculitis or phospholipid antibody syndrome
- Other systemic disorders that affect the kidney, including genetic disorders such as hereditary defects of GBM or podocyte genes leading to focal segmental glomerulosclerosis and hereditary tubulopathies or polycystic disorders; disorders driven by toxins, including Shiga toxin-producing *Escherichia coli*-induced HUS, drug- or contrast media-induced kidney injury; crystal and paraprotein-related nephropathies; and disorders caused by metals or food-borne toxins and toxic forms of focal segmental glomerulosclerosis
- Disorders that affect haemodynamics and the vascular system can also affect the kidney, including atherosclerosis, embolism, macro- or microvascular stenosis, shock, hepato-renal syndrome, thrombotic microangiopathy, eclampsia, hyperfiltration-associated focal segmental glomerulosclerosis, global glomerulosclerosis
- Obstructive nephropathy or renal amyloidosis

Tubules
Hairpin-like structures that receive filtered blood. The tubular epithelium reabsorbs water, electrolytes, nutrients and proteins. Each nephron has a single tubule, which defines proximal and distal tubules as parts of the nephron.

Chronic kidney disease
(CKD). Chronic (and often progressive) impairment of renal functions, such as blood purification, barrier function of the glomerular filter, water, electrolyte and acid–base homeostasis, endocrine functions such as vitamin D processing, erythropoietin production and blood pressure regulation.

Uraemia
End-stage chronic kidney disease, the treatment of which requires dialysis or kidney transplantation.

Glomerulonephritis
A heterogeneous group of immune-mediated kidney diseases that initiate in the glomeruli.

Podocyte
A visceral epithelial cell that covers the glomerular capillaries in the Bowman's capsule. Podocytes are a component of the glomerular filtration barrier.

Fibrocytes
Monocyte-derived collagen-producing cells that have been suggested to contribute to kidney fibrosis.

Kidney fibrosis
The end stage of chronic kidney disease, when functional renal tissue has been replaced by fibrotic scar tissue and is usually accompanied by uraemia.

the kidney proximal tubules, where >85% of the fluid is reabsorbed. Thus, renal DCs and the renal lymph nodes receive low-molecular-mass antigens from the circulation at concentrations that are over tenfold higher than in any other tissue. BATF3-dependent DCs in the renal lymph nodes capture and cross-present these proteins to $CD8^+$ T cells, which results in the programmed cell death 1 ligand 1 (PDL1)-mediated deletion of these T cells[21]. Thus, the renal lymph nodes have a special role in the development of immune tolerance against circulating innocuous low-molecular-mass proteins, such as food antigens and hormones.

Immune-mediated kidney disease

The kidneys are a frequent target of systemic immune and autoimmune disorders, including systemic autoimmunity and vasculitis, immune complex-related serum sickness and complement disorders. This is partly related to the size-selective and charge-dependent filtration process in the glomeruli that promotes glomerular immune complex deposition. In addition, immune responses against kidney-derived autoantigens can cause autoimmune kidney diseases.

In chronic kidney disease (CKD), low-molecular-mass compounds accumulate in the body, which causes uraemia. CKD affects approximately 10% of the Western population and is a serious social and economic burden, especially for those who progress to kidney failure and that require dialysis or transplantation. The tissue injury associated with CKD is commonly directly or indirectly caused by the immune system (BOX 2).

Direct immune-mediated injury often affects the glomeruli, at least initially, which causes different forms of glomerulonephritis. Irreversible kidney damage occurs when inflammation spreads to the tubulointerstitium[22–24]. Various mechanisms that cause this spreading have been proposed: podocyte damage might facilitate leakage of the glomerular filtrate and detachment of tubular cells from their basement membrane[25]; destruction of glomerular capillaries might restrict the perfusion of their downstream tubulointerstitial capillaries and cause ischaemia[26]; pro-inflammatory cytokines from inflamed glomeruli might perfuse the tubulointerstitial capillaries and cause inflammation[27]; reabsorption of abnormal amounts of protein from the glomerular filtrate might induce stress responses in tubular epithelial cells[28]; and glomerular antigens might reach DCs in the adjacent tubulointerstitium, which in turn might stimulate infiltrating T cells to produce pro-inflammatory cytokines[19]. Tubulointerstitial mononuclear cell infiltrates can contribute to continuing immunopathology and to progressive tissue remodelling, which lead to tubular atrophy and interstitial scarring, both by maintaining local chronic inflammation and by recruiting fibrocytes[29]. The end state of CKD is kidney fibrosis — a state in which functional nephrons are replaced by fibrotic tissue.

Immune-mediated CKD can be induced by immune complex deposition, by innate immunity and by T cells that interact with kidney-resident immune cells. Importantly, these immune mechanisms generally contribute to the progression of CKD, even in non-immune-initiated forms of the disease, and therefore there are obvious implications for therapy.

Inflammasome
An intracellular complex containing pattern recognition receptors that activate caspase 1. Caspase 1 activation induces pyroptotic cell death and interleukin-1β (IL-1β) and IL-18 secretion.

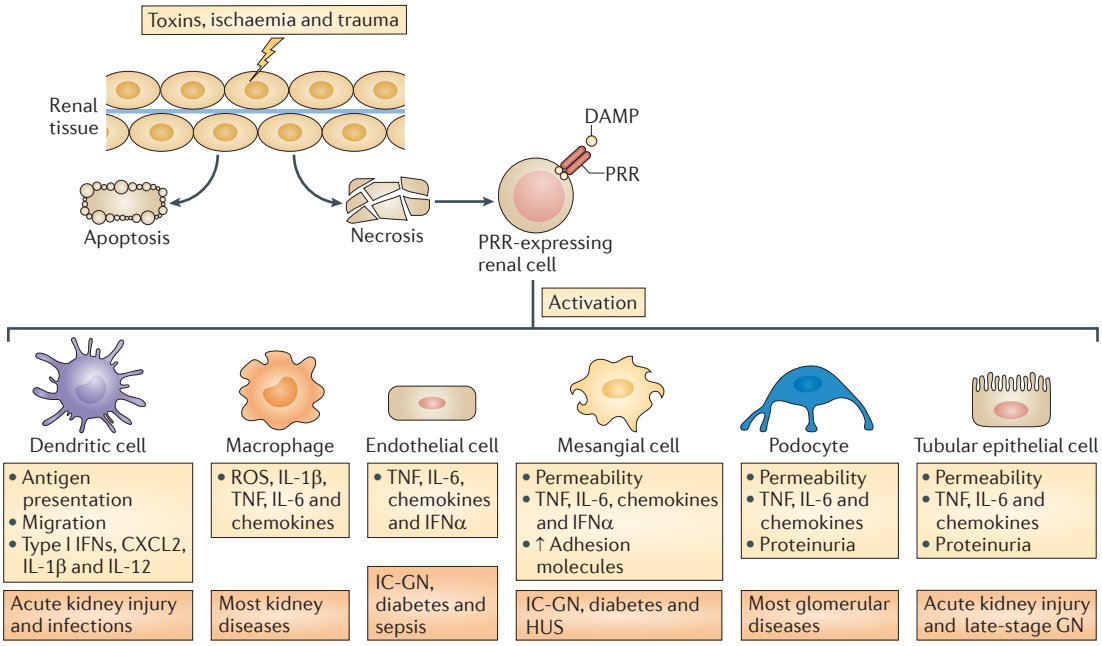


Figure 1 | **Innate immune mechanisms in kidney inflammation.** Renal cell necrosis or programmed forms of inflammatory cell death release damage-associated molecular patterns (DAMPs) into the extracellular space, where they activate pattern recognition receptors (PRRs). Renal dendritic cells and macrophages express numerous PRRs, whereas PRR expression is limited on renal non-immune cells. PRR ligation activates the cell, which results in cell type-specific consequences, such as the secretion of pro-inflammatory mediators that promote renal immunopathology. In the glomerulus, PRR activation in mesangial cells also stimulates their proliferation, for example, in mesangioproliferative forms of glomerulonephritis such as lupus nephritis, IgA nephropathy and hepatitis C virus-associated glomerulonephritis. PRR activation of endothelial and epithelial cells (including podocytes and tubular epithelial cells) in the glomerulus increases their permeability, which results in proteinuria, a clinically useful biomarker of glomerular vascular permeability, inflammation and damage. Moreover, the activation of endothelial and epithelial cells manifests as interstitial oedema and secretory dysfunction, for example, in septic acute kidney injury. CXCL2, CXC-chemokine ligand 2; GN, glomerulonephritis; HUS, haemolytic uraemic syndrome; IC-GN, immune complex glomerulonephritis; IFN, interferon; IL, interleukin; ROS, reactive oxygen species; TNF, tumour necrosis factor.

Innate immune responses in CKD. Clinical entities of kidney disease, such as post-ischemic and toxic acute kidney injury, as well as nephropathies that are induced by diabetes, hypertension and crystal deposition, involve sterile inflammation. As in other organs, sterile renal inflammation is induced by intrinsic damage-associated molecular patterns (DAMPs) that are either released from dying parenchymal cells or that are generated during extracellular matrix remodelling[30–33]. The kidney hosts a large range of different parenchymal cell types, including tubular epithelial cells, and endothelial cells that express a subset of Toll-like receptors (TLRs; that is, TLR1 to TLR6) and inflammasome components, which suggests that these cells can respond to DAMPs and that they can induce innate immune responses and subsequent renal inflammation[34]. However, NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome activation is limited to renal mononuclear phagocytes. The resulting inflammation depends on the nature of the stimulus (whether it is transient, repetitive or persistent) and the renal compartment that is affected (FIG. 1); for example, glomerular deposition of antibodies or immune complexes and the activation of complement and Fc receptor signalling drives the several forms of immune complex glomerulonephritis that have been described (BOX 2; see below).

By contrast, ischaemia, toxins, crystals and urinary outflow obstruction target the tubulointerstitial compartment, in which they drive sterile inflammation. Renal tubular epithelial cells are highly susceptible to intrinsic oxidative stress because of their high reabsorptive and secretory activity and because their capillary network is downstream of the glomerular capillaries, which renders the medullary part of the tubulointerstitium susceptible to hypoxia, as occurs during renal hypoperfusion and shock. During sepsis and ischaemia–reperfusion injury, necrotic tubular cells and neutrophils release high-mobility group box 1 protein (HMGB1), histones, heat-shock proteins, hyaluronan, fibronectin, biglycan and other DAMPs that activate TLR2 and TLR4 on renal parenchymal cells and renal DCs. Renal parenchymal cells and DCs then secrete chemokines that promote an acute neutrophil-dependent inflammatory response that mainly contributes to acute kidney injury[35–37]. Another important DAMP is ATP that triggers sterile inflammation in the kidneys via the NLRP3 inflammasome[38]. By contrast, adenosine receptor A2a signalling inactivates DCs and abrogates kidney injury[39]. The DAMP T cell immunoglobulin and mucin domain-containing protein 1 (TIM1; also known as kidney injury molecule 1) is induced on the

surface of tubular epithelial cells and binds to CD300b (also known as CLM7) on myeloid cells, which drives neutrophil recruitment to the post-ischemic kidney[31]. The initial inflammatory response is amplified by infiltrating neutrophils and later by LY6C^{hi} macrophages, which results in acute kidney injury. The cellular pathophysiology of ischemic acute kidney injury has recently been reviewed by others[40].

Tubular cells are especially sensitive to the freely filtered low-molecular-mass toxins that they reabsorb from the tubular fluid. These toxins can accumulate and induce tubular cell necrosis and subsequent TLR4-mediated tubulointerstitial inflammation[41]. The high osmolarity and varying pH of urine promotes the crystallization of small filtered molecules, such as uric acid, calcium oxalate, calcium phosphate, myoglobin and free immunoglobulin light chains in the tubules. The crystals obstruct the tubules and directly injure the epithelial cells that line them, which indirectly causes sterile inflammation; examples of such crystalline nephropathies include kidney stone disease, oxalate nephropathy, acute urate nephropathy, adenine nephropathy, cystinosis, rhabdomyolysis-induced acute kidney injury and myeloma-associated cast nephropathy. A recently discovered pathological mechanism of sterile renal inflammation is that crystals that reach the tubulointerstitial compartment can directly induce inflammation by activating the NLRP3 inflammasome in renal DCs[34]. In addition, urinary outflow obstruction causes renal sterile inflammation through multiple mechanisms. It remains to be clarified which kidney diseases will benefit most from selective therapeutic blockade of these aforementioned innate immune pathways. Persistent renal inflammation is usually associated with epithelial atrophy and aberrant mesenchymal cell repair, which is known as glomerulosclerosis or interstitial fibrosis. The direct contribution of innate immune responses to progressive fibrosis remains an area of debate[33,42]. In addition, NLRP3 has inflammasome-independent effects in the tubular epithelium; for example, NLRP3 and the adaptor molecule ASC are needed for SMAD2 and SMAD3 phosphorylation in response to transforming growth factor-β receptor 1 (TGFβR1) signalling[43–45]. As TGFβR1 signalling is an essential pathway for epithelial–mesenchymal transition and renal fibrosis, this non-canonical effect of NLRP3 contributes to renal scarring. Whether this process also contributes to other forms of CKD remains to be studied.

Uromodulin (also known as Tamm–Horsfall protein) is a kidney-specific molecule that is synthesized by epithelial cells in the distal tubules and that is selectively released into the tubular lumen. Uromodulin is an adherent polymer that binds to particles, pathogens, crystals and cytokines in the urine and facilitates their elimination. Uromodulin deficiency aggravates urinary tract infections, crystal aggregation and cytokine-mediated luminal inflammation in the kidneys[46]. Uromodulin leaks into the interstitium after tubular injury and activates intrarenal DCs and blood monocytes via TLR4 and the NLRP3 inflammasome in a DAMP-like manner[47,48]. This provides another example of endogenous molecules that function as immunostimulatory danger signals when they escape their normal physiological compartment; uromodulin may also contribute to the systemic inflammation associated with CKD.

Taken together, these findings show that non-infectious triggers induce innate immune responses in the kidney that can cause inappropriate immunopathology. Distinct immune pathways contribute to certain types of renal sterile inflammation such as the NLRP3 inflammasome in crystalline nephropathies. It remains necessary to identify the predominant pathways in each of the many different kidney diseases. Furthermore, the non-canonical function of NLRP3 during TGFβ1R signalling that was first described in kidney disease not only awaits validation in systemic immune regulation but also deserves further study in different renal epithelial cell types.

Complement dysregulation and CKD. Recent advances in complement biology have led to the reclassification of glomerular diseases that are characterized by complement deposition in the absence of concomitant antibody deposition[49,50]. Complement C3 glomerulopathies are caused by spontaneous and uncontrolled activation of the alternative complement pathway because of mutations in the components or the molecules that regulate it, such as factor B, factor H, factor I, membrane cofactor protein and factor H-related proteins[51–54]. An autoimmune variant of C3 glomerulopathy is mediated by an autoantibody (known as C3 nephritic factor) that is specific for C3 convertase. C3 nephritic factor stabilizes the C3 convertase, which leads to unrestrained complement activation and the subsequent deposition of C3 in the kidneys, which is accompanied by variable pathomorphological findings (most often membranoproliferative changes). The importance of recognizing C3 glomerulopathies as a separate clinical entity is emphasized by initial reports that indicate the effectiveness of treatment with the C5 inhibitor eculizumab (Soliris; Alexion Pharmaceuticals)[55–57].

Thrombotic microangiopathy (TMA) is characterized by microvascular injury and thrombosis, which results in haemolytic anaemia with erythrocyte fragmentation, thrombocytopenia and organ dysfunction. The kidney and brain are primarily affected by this disease and the functional impairment in these organs mainly determines the outcome of the patients. The classification, pathogenesis and treatment strategies of TMA remain controversial. Three major types of TMA are commonly identified: two forms of haemolytic uraemic syndrome (HUS), including Shiga toxin-producing *Escherichia coli*-induced HUS (STEC-HUS) and atypical HUS (aHUS), as well as thrombotic thrombocytopenic purpura (TTP). Recent studies have improved our knowledge of all three groups of disease.

Infection with Shiga toxin-producing *E. coli*, which cause haemorrhagic enteritis, is the most common cause of HUS in children. After translocation across the intestinal epithelium, the Shiga toxin is transported in the circulation by poorly defined mechanisms to capillary beds in target organs. In the kidneys, Shiga toxin binds to the

Haemolytic uraemic syndrome
(HUS). A group of diseases, which are induced by infection with Shiga toxin-producing bacteria, or by genetic or acquired defects in complement regulators, that are characterized by microvascular injury and thrombosis, which results in haemolytic anaemia, thrombocytopenia and organ dysfunction (kidney and often brain).

Thrombotic thrombocytopenic purpura
(TTP). A rare life-threatening disease, characterized by the development of platelet thrombi and microvascular injury, which results from either genetic or acquired defects of the enzyme a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which has a unique role in the homeostasis of the coagulation system.

glycolipid receptor globotriaosylceramide (Gb3), which is highly expressed on the glomerular endothelium, thereby initiating the events that are responsible for microvascular cell injury. Shiga toxin directly induces the expression of P-selectin on human endothelial cells, and P-selectin then binds to and activates complement C3 via the alternative complement pathway, which leads to thrombus formation in the microvasculature[58]. This can be prevented by treatment with a C3a receptor antagonist in a mouse model of STEC-HUS[58]. Children with STEC-HUS have complement hyperactivation[59], and early reports document marked improvement in small numbers of patients shortly after treatment with eculizumab[60]. This is supported by a clinical study that used eculizumab during the major STEC-HUS outbreak in northern Germany in 2011 (R. A. K. Stahl, personal communication).

Complement is also central to the pathogenesis of aHUS, which is a rare group of disorders that includes sporadic and familial diseases and that is often caused by uncontrolled complement activation as a result of innate or acquired defects in the regulatory components of the complement system. In particular, mutations in the genes that encode factor H, membrane cofactor protein, factor I and thrombomodulin have a crucial role in aHUS[61]. Interestingly, the same mutations underlie C3 glomerulopathy (see above). Eculizumab has become the first-line therapy in aHUS[62]. How similar and/or identical defects in regulatory proteins of the alternative complement pathway lead to a range of phenotypical manifestations of systemic and renal disease remains to be fully elucidated.

TTP has been linked to reduced activity of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which results from either genetic or a cquired defects, including the generation of ADAMTS13-specific autoantibodies. Reduced ADAMTS13 activity leads to the disruption of von Willebrand factor-multimer processing, the development of platelet thrombi and microvascular injury[63].

The major advances in the field of C3 glomerulopathy and thrombotic microangiopathies now provide the basis for a new pathogenesis-based disease classification, and complement dysregulation is likely to be a general feature in all of these disease entities. Most importantly, this gain in understanding has resulted in the use of terminal complement inhibition as a first-line therapy in aHUS, and might also result in its use in the other forms of HUS in certain circumstances in the future[61]. Moreover, hyperactivation of C5a and its receptor may also be involved in other renal autoimmune diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis[64].

T cell responses targeting the kidney

DTH in crescentic glomerulonephritis. Glomerular crescents, formed by proliferation of the glomerular parietal epithelial cells and infiltrating leukocytes, are the morphological hallmarks of the most aggressive form of glomerulonephritis that progresses rapidly towards kidney failure. Despite being first described 100 years ago, nephrotoxic nephritis remains one of the most widely studied mouse models of crescentic glomerulonephritis. It is induced by injecting mice with heterologous antibodies specific for the glomerular basement membrane (GBM) (Supplementary information S1 (table)). Injury in this model was initially thought to be exclusively mediated by antibodies[65]. Subsequent studies suggested that there might also be roles for antigen-specific T cells[66–68], and Holdsworth and colleagues[69] established that T cell-dependent delayed-type hypersensitivity (DTH) responses to the heterologous immunoglobulins deposited in the kidney were an underlying mechanism of injury (FIG. 2).

Recent studies showed the following sequence of events to take place. In the first days following antibody injection, innate immune cells, including neutrophils, mast cells[15] and interleukin-17 (IL-17)-producing γδ T cells[70], mediate renal damage. T cells specific for the heterologous antibodies are simultaneously primed in the lymphatic tissues and start entering the kidneys. A first wave of T cells, starting 4 days after nephritis induction, consists of pathogenic T helper 17 (T_H17) cells expressing CC-chemokine receptor 6 (CCR6) and retinoic acid receptor-related orphan receptor-γt (RORγt)[71-74]. Their activity is controlled by CXC-chemokine receptor 6 (CXCR6)-expressing regulatory invariant natural killer T (iNKT) cells, which are recruited by immature renal DCs secreting CXC-chemokine ligand 16 (CXCL16)[75]. If inflammation fails to resolve, renal DCs eventually mature and recruit $CXCR3^+$ T_H1 cells by producing CXCL9 (REFS 76,77). T_H1 cells encounter antigens presented by DCs in the context of upregulated co-stimulatory molecules and IL-12. Next, activated T_H1 cells recruit more pro-inflammatory cells, including monocytes and fibrocytes[29], and stimulate mannose receptor-dependent macrophages[78] to produce injurious mediators such as tumour necrosis factor (TNF) and nitric oxide[69,72]. As renal DCs are located in the interstitium but not within the glomeruli, the stimulation of T_H1 cells takes place in the periglomerular space, adjacent to parietal epithelial cells. The proliferative response of parietal epithelial cells and immune cells contributes to the characteristic glomerular crescents. $CCR6^+$ and $CCR7^+$ regulatory T (T_{Reg}) cells may still be able to control inflammation at this stage[79–81]. The severity of the initial injury determines the balance between pro-inflammatory and anti-inflammatory T cells in the tissue, and whether kidney disease resolves or progresses to fibrosis. After 14 days, host antibodies that have been raised against the heterologous antibodies increasingly contribute to kidney injury.

Although immunity in nephrotoxic nephritis is directed against a different antigen than in human crescentic glomerulonephritis, this model has been instrumental in elucidating the mechanisms that drive immune responses to glomerular antigens and has made crucial contributions to the design of novel therapies. However, the extent to which DTH is also responsible for human crescentic glomerulonephritis remains uncertain. Furthermore, it would be desirable to study whether these cellular immune mechanisms are also relevant in other forms of glomerulonephritis.

Anti-neutrophil cytoplasmic antibody
(ANCA). An autoantibody that is commonly found in pauci-immune focal necrotizing glomerulonephritis.

Crescentic glomerulonephritis
A rapidly progressive form of glomerulonephritis characterized by the hyperproliferation of parietal epithelial cells, which is driven by T cell and macrophage infiltrates and by plasma components leaking through the glomerular filter.

Delayed-type hypersensitivity
(DTH). An inappropriate T cell-initiated response to self or foreign antigens that is carried out by macrophages, eosinophils or cytotoxic T cells.

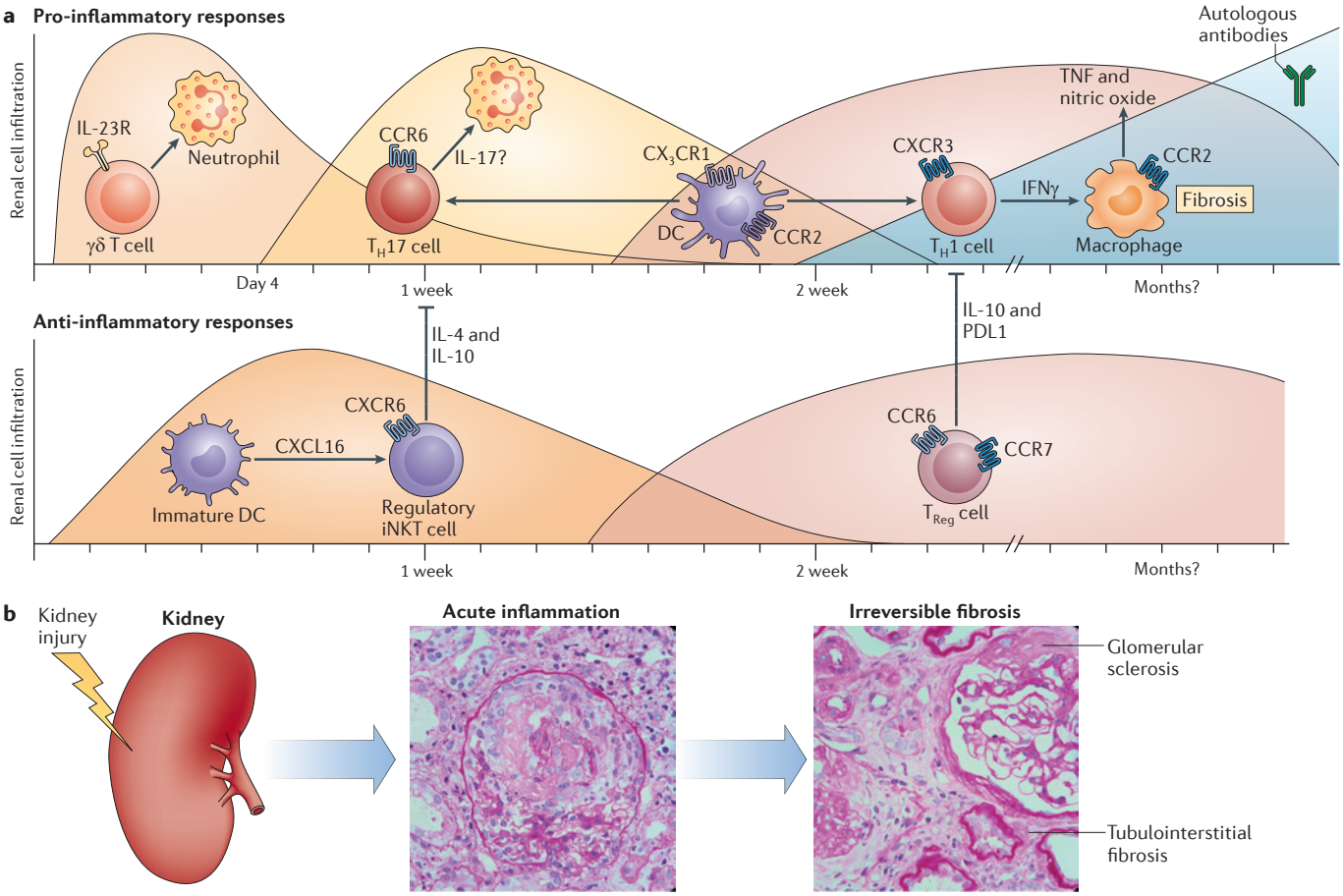


Figure 2 | **Cellular immune response in experimental crescentic glomerulonephritis.** The time-dependent changes in the pro-inflammatory and anti-inflammatory functions of leukocyte subsets during the course of experimental crescentic glomerulonephritis (a nephrotoxic nephritis model) are shown. **a** | The clinical outcome of the disease mainly depends on the balance between pro-inflammatory and anti-inflammatory immune cells. Whether this concept is relevant to human crescentic glomerulonephritis remains to be shown. Neutrophil recruitment to the kidney starts several hours after the induction of nephrotoxic nephritis and is partly mediated by interleukin-17A (IL-17A)-producing γδ T cells, which are activated by IL-23. The adaptive immune response is initiated by mature dendritic cells (DCs) that depend on CX_3C-chemokine receptor 1 (CX_3CR1) and CC-chemokine receptor 2 (CCR2). At earlier stages, immune responses that are mediated by CCR6-expressing T helper 17 (T_H17) cells predominate, whereas at later stages, CXC-chemokine receptor 3 $(CXCR3)^+$ T_H1 cells are the prevailing mediators of renal tissue injury, as they produce cytokines such as interferon-γ (IFNγ), which activate macrophages. In addition, host antibodies against the heterologous antibodies form intrarenal immune complexes and thereby contribute to renal tissue damage. During the first days immature DCs attenuate crescentic glomerulonephritis by attracting regulatory invariant natural killer T (iNKT) cells via the CXC-chemokine ligand 16 (CXCL16)–CXCR6 axis, and these cells produce IL-4 and IL-10 and thereby might reduce the destructive T_H1 and T_H17 cell responses. At a later stage, $CCR6^+$ and $CCR7^+$ regulatory T (T_{Reg}) cells are recruited into the inflamed kidney and protect against an overwhelming T_H1 cell- and T_H17 cell-mediated immune response, at least partly through the local production of IL-10 and the expression of programmed cell death 1 ligand 1 (PDL1). **b** | Periodic acid-Schiff (PAS) staining of kidney sections from patients with acute crescentic glomerulonephritis shows glomerular and tubulointerstitial leukocyte infiltration. Irreversible kidney damage occurs along with glomerular sclerosis and tubulointerstitial fibrosis when the inflammatory response persists. IL-23R, IL-23 receptor; TNF, tumour necrosis factor. Image courtesy of U. Helmchen, Hamburg, Germany.

T cell-mediated glomerular injury. The role of T cells in renal injury has long been controversial[65–67]. A recent study using transgenic mice showed that adoptively transferred $CD4^+$ T_H cells and cytotoxic $CD8^+$ T cells that are specific for glomerular antigens can injure the kidneys[19]. The resulting release of glomerular antigens starts a vicious circle involving antigen capture and presentation by renal DCs to T_H cells, the production of chemokines and cytokines, the recruitment of more $CD8^+$ T cells and macrophages, and increased renal damage.

These findings, together with those in nephrotoxic nephritis, emphasize the importance of crosstalk between mature renal DCs and T_H cells; in both cases the removal of kidney DCs in mice by depletion[19,82], by CX_3CR1 blockade or by genetic knockout[9,83] rapidly reduced the mononuclear cell infiltration and halted disease progression. Although the route by which glomerular antigens reach DCs in the tubulointerstitium is still unclear, their ability to do so and to stimulate T_H cells may contribute to the spreading of glomerular

injury to the tubulointerstitium[68], and therefore may represent a mechanism of kidney disease progression. However, the relevance of these immune mechanisms for human glomerulonephritis remains to be shown. In particular, the role of cytotoxic T lymphocytes (CTLs) in human nephritis is unclear. In addition, the (auto) antigens presented to T_H cells remain to be identified. Finally, intrinsic renal cells, such as glomerular podocytes[84] and tubular epithelial cells[85], can also present antigen to T cells, but the *in vivo* relevance of these processes is unclear.

Proteinuria. Damage to the glomerular filtration barrier causes protein to leak into the glomerular filtrate, which results in abnormally high concentrations in the urine: this is known as proteinuria. Proteinuria can itself cause injury, which is mediated either by the properties of specific proteins in the filtrate or simply through the mass of filtered protein; for example, fibrin can induce the proliferation of parietal glomerular epithelial cells and thus can aggravate crescentic glomerulonephritis[86]. Increased protein in tubular fluid enhances reabsorption by the tubular epithelial cells and can overload their catabolic capacity, which results in a lysosomal burst and the release of cathepsins into the cytoplasm[28]. Filtered complement components, especially properdin (also known as factor P), contact the tubular epithelial cells and activate the alternative complement pathway that damages tubular cells[87,88]. Tubulointerstitial DCs capture filtered proteins, either directly or from tubular cells, and use them to locally stimulate infiltrating CTLs or T_H cells[82,89]. Such presentation of antigens that would normally be ignored may contribute to the infiltration of immune cells into the tubulointerstitium and to the progression of renal disease, but the relevance of this mechanism to human kidney disease remains to be shown. Regardless of the mechanisms involved, non-specifically reducing proteinuria — for example, by lowering glomerular filtration pressure by the pharmacological inhibition of the renin–angiotensin system — has become an important therapeutic concept.

Antibody-dependent kidney diseases

Rodent studies have increased our understanding of the nature of the immune responses in the kidneys and how they are subverted to cause injury. Furthermore, the examination of the patterns of immunoglobulin deposition in the kidneys initiated the ultimately successful search for autoantibodies in human anti-GBM disease and membranous nephropathy and lead to the characterization of the glomerular antigens they recognize.

Anti-GBM disease. Anti-GBM disease, formerly known as Goodpasture's disease, is a severe form of crescentic glomerulonephritis that is caused by autoantibodies specific for the non-collagenous 1 (NC1) domain of the α3 chain of type IV collagen (α3(IV)NC1) in the GBM[90,91]. Type IV collagen in the GBM consists of α3, α4 and α5 chains, the NC1 domains of which form hexamers that are stabilized by sulfilimine bonds[92]. Pathogenic autoantibodies bind to two dominant epitopes on the α3(IV)NC1 domain (EA-α3 and EB-α3), and to a homologous epitope on the α5(V1)NC1 domain (EA-α5)[92]. Although they are freely accessible in individual NC1 domains, all three epitopes are hidden in the hexamers and so are unavailable for antibody binding in the intact GBM. A conformational change in NC1 hexamers within the GBM is required to expose the epitopes and to facilitate autoantibody binding, which then amplifies further conformational changes and autoantibody binding. This may be an explanation for the rapid development of the injury in this disease. By contrast, GBM-specific alloantibodies that develop after transplanting a normal kidney into α5(IV)NC1-deficient mice recognize epitopes on the surface of the NC1 hexamer and bind to them without the need for conformational change[93].

Susceptibility to anti-GBM disease is strongly influenced by the HLA class II haplotype: over 80% of those affected carry the HLA-DRB1*15:01 allele[94]. The direct involvement of HLA-DRB1*15:01 in the specific autoimmune response to α3(IV)NC1 has been confirmed *in vitro* using human T cells[95,96] and in transgenic mice that only express HLA-DRB1*15:01 (REF. 97). The naturally processed α3(IV)NC1 peptides that were bound to HLA-DRB1*15:01 on antigen-presenting cells have been characterized[98] but T cells from patients with anti-GBM disease fail to respond to them. These peptides are fairly resistant to antigen-processing enzymes, whereas the four epitopes that are commonly recognized by the patients' T cells are rapidly digested[95,96]. This may be an explanation as to why NC1-specific autoreactive T cells in patients with this disease escape thymic deletion.

Rodent models of autoimmune anti-GBM disease resemble the human clinical disease and are driven by similar α3(IV)NC1 epitopes[90,97], but DTH rather than antibodies cause the severe injury, at least in mice[81,91]. It remains to be seen whether the contribution of DTH to injury in anti-GBM disease has been underestimated in humans; indeed, T_H1 cells that are specific for α3(IV)NC1 predominate in the acute phase of anti-GBM disease in humans but they are replaced by an antigen-specific IL-10-producing T_{Reg} cell response that coincides with a reduction in anti-GBM antibody levels and with reduced disease activity[90,95].

PLA2R-specific antibodies in membranous nephropathy. Membranous nephropathy is a major cause of glomerulonephritis with nephrotic syndrome in adults. It is characterized by the thickening of the GBM and the deposition of immune complexes between the membrane and the podocytes. Approximately 75% of cases are idiopathic and 25% are secondary to a wide range of causes, including neoplasia, infections, drugs and systemic autoimmune disease. Classic studies using the Heymann nephritis model of membranous nephropathy (Supplementary information S1 (table)) showed that circulating antibodies that are specific for megalin (also known as LRP2) — a protein that is expressed on the surface of glomerular podocytes — promote the formation of immune complexes in the kidneys[99]. However, human podocytes lack megalin.

Proteinuria
The urinary loss of protein, which has numerous clinical consequences. Proteinuria is also used as a biomarker for renal filter dysfunction.

Anti-GBM disease
(Anti-glomerular basement membrane disease; also known as Goodpasture's disease). A severe form of crescentic glomerulonephritis caused by autoantibodies that are specific for the NC1 domain of the α3 chain of type IV collagen (α3(IV)NC1) in the GBM.

Membranous nephropathy
A glomerulonephritis form characterized by the subepithelial deposition of secretory phospholipase A2 receptor (PLA2R)-specific antibodies, which leads to podocyte injury and heavy proteinuria. It is the most common cause of the nephrotic syndrome in adults.

Nephrotic syndrome
A syndrome characterized by heavy proteinuria, hypoalbuminaemia and a loss of immunoglobulins, which results in humoral immunodeficiency, oedema, hyperlipidaemia and thrombosis. This syndrome results from damage to the glomerular filter, which causes the loss of proteins above 50 kDa in size from the circulation.

The autoantigen in human idiopathic membranous nephropathy was recently identified as secretory phospholipase A2 receptor (PLA2R; also known as CLEC13C) on podocytes[100]. PLA2R-specific autoantibodies, usually of the IgG4 subclass, were found in the serum of 50–70% of patients with primary membranous nephropathy. Subsequent studies showed that the levels of PLA2R-specific autoantibodies correlate with the level of proteinuria and could possibly be used to predict clinical outcome[100] and disease recurrence after renal transplantation[101]. So far, there is no proof that PLA2R-specific autoantibodies are pathogenic, but a genome-wide association study has shown that *PLA2R1* polymorphisms influence susceptibility to idiopathic membranous nephropathy[102]. This study also confirmed that there is a strong association between the disease and certain HLA-DQA1 alleles, which suggests that these HLA class II molecules may facilitate autoimmunity against PLA2R[102]. However, as only 50–70% of patients with primary membranous nephropathy have PLA2R-specific autoantibodies, additional autoantigens remain to be identified. Moreover, the pathophysiological role of PLA2R-specific autoantibodies is still unknown.

IgA nephropathy. IgA nephropathy is the most common primary form of glomerulonephritis and is an important cause of kidney failure. Recent studies suggest that a multistep process is involved in the immunopathogenesis of this disease. B cells from patients with IgA nephropathy produce aberrantly glycosylated IgA[103], possibly as a consequence of the aberrant homing of mucosal B cells to the bone marrow, where they synthesize under-galactosylated IgA. Patients with IgA nephropathy develop autoantibodies against under-galactosylated IgA, which might also cross-react with mucosal microbial antigens, although this has not been formally shown. These autoantibodies form immune complexes in the circulation, which are then deposited in the glomerular mesangium by mechanisms that are so far incompletely understood[104]. The deposited immune complexes induce the local expression of pro-inflammatory mediators and growth factors, which activate mesangial cells and enhance their secretion of extracellular matrix proteins, which leads to glomerular sclerosis and loss of renal function. The presence of IgG and IgA glycan-specific autoantibodies was shown to correlate with progressive disease in a large group of patients[105], which suggests that these glycan-specific autoantibodies are potentially pathogenic. However, the factors that are responsible for the synthesis of under-galactosylated IgA, autoantibody generation, mesangial deposition of immune complexes and injury remain elusive.

Lupus erythematosus. The extrarenal mechanisms of lupus nephritis involve complex genetic variability that compromises immune tolerance to nuclear autoantigens[106–108]. The nucleic acid components of nuclear autoantigens support this process via their TLR-dependent autoadjuvant effects[109–111]. As such, endogenous nuclear particles are handled as viral particles and induce interferon-α signalling[112,113], which is similar to viral infections[114,115]. The link between systemic lupus erythematosus and lupus nephritis is the production of autoantibodies that bind to autoantigens in the kidneys; for example, a subset of double-stranded DNA (dsDNA)-specific antibodies cross-react with annexin II on the cell surface, in the cytoplasm and in the nucleus of mesangial cells[116], and also cross-react with nucleosomes in the mesangium and in the glomerular capillary epithelium[117]. The extent and the progression of glomerular immunopathology depends on the site of immune complex formation, as this determines the predominant glomerular cell type that is affected[118] (FIG. 3).

Pauci-immune focal necrotizing glomerulonephritis. Pauci-immune focal necrotizing glomerulonephritis (FNGN) is a systemic autoimmune disease that is characterized by crescentic glomerulonephritis. It typically occurs in the context of systemic small vessel vasculitis and autoantibodies that bind to neutrophil cytoplasmic antigens specific for either myeloperoxidase (MPO) or proteinase 3 (PR3; also known as myeloblastin)[119]. Most patients with pauci-immune FNGN also have autoantibodies to lysosome-associated membrane glycoprotein 2 (LAMP2)[120,121], although the frequency of these antibodies is controversial[122]. All three target antigens are released into injured glomeruli by infiltrating neutrophils after degranulation or through NETosis[123]. LAMP2 is also expressed on the surface of the glomerular endothelium[108]. Injury is thought to be autoantibody mediated, not least because B cell ablation with rituximab is a highly effective treatment for pauci-immune FNGN[119] (TABLE 1). Despite this, deposits of immunoglobulin and complement components in pauci-immune FNGN are small and restricted to necrotic areas of the kidneys. The role of complement is being re-evaluated in Phase I clinical trials of complement inhibitors because patients with clinically active disease have systemic complement activation[124,125]. Finally, there is evidence that cell-mediated immunity is also involved[126]: lymphocytes infiltrate the glomeruli and the tubulointerstitium[127], and there are circulating MPO-specific and PR3-specific T_H1 and T_H17 cells in patients with pauci-immune FNGN[126]. Furthermore, $CD8^+$ T cells are increased and express a transcriptomic signature that correlates with the risk of disease relapse[128].

Clinical[119] and genetic[129] studies combined with *in vitro* experiments[130] and rodent models[131] provide compelling evidence that MPO-specific and PR3-specific autoantibodies can be pathogenic. Mice that have been injected with antibodies specific for MPO develop pauci-immune FNGN, although injury is mild in most mouse strains unless the antibody is administered together with a neutrophil-activating factor such as TNF, C5a or IL-1 (REFS 130,131). This facilitates binding of the antibodies to circulating neutrophils and promotes their glomerular localization with the release of MPO[132]. Attempts to induce pauci-immune FNGN in mice with PR3-specific antibodies have been unsuccessful[130,131], except in a single report in which PR3-specific autoantibodies from a patient with pauci-immune FNGN were injected into humanized mice[133]. This possibly reflects the differences in PR3 expression by human and mouse neutrophils[125,131].

IgA nephropathy
The most common form of glomerulonephritis worldwide. It is characterized by the deposition of IgA-containing immune complexes in the mesangial compartment of glomeruli, which leads to mesangial cell-proliferative lesions, haematuria and proteinuria.

Pauci-immune focal necrotizing glomerulonephritis
(Pauci-immune FNGN). A highly inflammatory form of glomerulonephritis in which glomerular immune complex deposits are absent or scarce. It is commonly associated with small vessel vasculitis and with anti-neutrophil cytoplasmic antibodies.

NETosis
The formation and the release of neutrophil extracellular traps (NETs) by activated neutrophils to ensnare invading microorganisms. NETs enhance neutrophil killing of extracellular pathogens while minimizing damage to the host cells.

Humanized mice
Immunodeficient mice that are engrafted with human haematopoietic cells or tissues, or mice that transgenically express human genes.

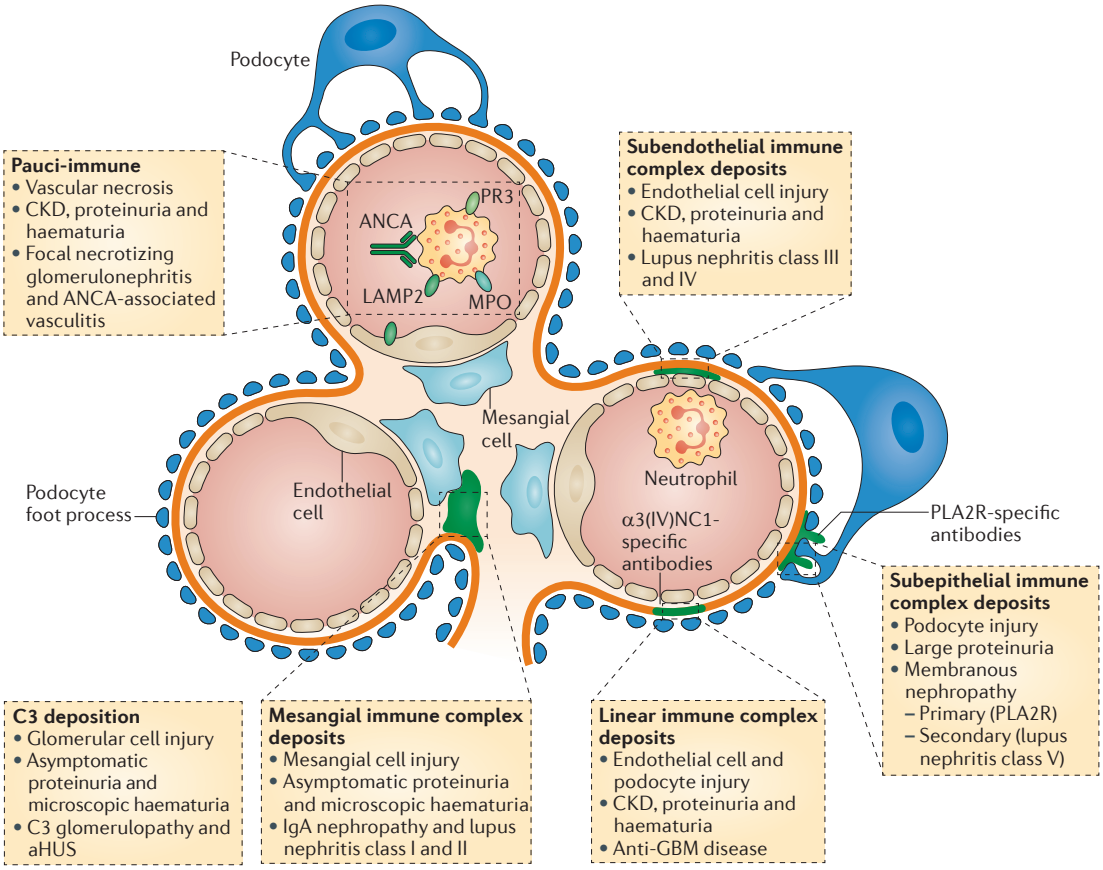


Figure 3 | **Local immune pathways in glomerulonephritis.** Glomerular immunopathology often develops from intraglomerular complement activation via the classical (immune complex-related) or alternative (immune complex-independent) complement pathway. Immune complexes can form in different compartments of the glomerulus, which determines the resulting histopathological lesion, as different glomerular cell types are primarily activated in each compartment. The resulting histopathological lesions determine the classification of glomerulonephritis. Immune complex deposition in the mesangium activates mesangial cells, which leads to mesangioproliferative glomerulopathies, such as IgA nephropathy or lupus nephritis class I and II. Subendothelial immune complex deposits activate endothelial cells, as seen in lupus nephritis class III and IV. Subepithelial immune complex deposits preferentially activate the visceral glomerular epithelium — that is, podocytes — and usually cause massive proteinuria, as these cells are essential for the glomerular filtration barrier. As a result of the poor regeneration of podocytes compared with that of the other glomerular cell types, podocyte loss leads to progressive membranous nephropathy and end-stage renal disease. Primary membranous nephropathy mainly develops from autoimmunity against PLA2R, whereas secondary forms of this nephropathy represent renal manifestations of systemic disorders such as lupus nephritis. Hence, the level of proteinuria is an important prognostic biomarker and predictor of poor outcomes of glomerulopathies. Linear immune complex deposits indicate antibody binding to autoantigens within the glomerular basement membrane (GBM), for example, collagen IV antibodies in anti-GBM disease. Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis develops in the absence of immune complex deposits (known as pauci-immune), as it is driven by both ANCAs and cellular immunity. Complement component C3 glomerulopathies and atypical haemolytic uraemic syndrome (aHUS) develop from the aberrant activation of the alternative complement pathway. The boxes list in order the type of immune deposits, the glomerular structure that is primarily affected, the dominant clinical signs and the related disorders for each mechanism. α3(IV)NC1, non-collagenous 1 (NC1) domain of the α3 chain of type IV collagen; CKD, chronic kidney disease; LAMP2, lysosome-associated membrane protein 2; MPO, myeloperoxidase; PLA2R, secretory phospholipase A2 receptor; PR3, proteinase 3.

Antibodies that are specific for recombinant human LAMP2 bind to the glomerular endothelium and cause pauci-immune FNGN when they are injected into Wistar-Kyoto rats[120].

Mice that have been immunized with MPO develop autoantibodies and DTH responses characterized by T_H1 and T_H17 cells, but they remain healthy even in the absence of autoimmune regulator (AIRE) — which is expressed by medullary thymic epithelial cells and which promotes the expression of tissue-specific antigens (including MPO) that regulate central tolerance to these antigens — and despite the abundance of MPO in thymic myeloid cells[134,135]. Mice with autoimmunity to MPO remain healthy but develop severe pauci-immune FNGN in response to injection of GBM-specific antibodies at levels below the threshold required to cause kidney tissue

Table 1 | **Implementation of immunosuppressive or anti-inflammatory therapies in the treatment of kidney diseases**

Target	Drugs	Effective in animal kidney disease models?	Effective in human kidney disease?
IL-1	IL-1-specific antibody or recombinant IL-1RA	Oxalate nephropathy, IgA nephropathy and anti-GBM disease	Unknown
IL-6	IL-6-specific antibody	Lupus nephritis, anti-GBM disease and immune complex glomerulonephritis	Unknown
IL-17	IL-17-specific antibody	Crescentic glomerulonephritis	Unknown
TNF	TNF-specific antibody or TNFR–Fc fusion protein	Lupus nephritis, anti-GBM and ANCAs, glomerulonephritis, glomerulosclerosis and acute kidney injury	• TNF-specific antibody was effective in severe lupus nephritis, but had side effects • The TNF inhibitor etanercept (Enbrel; Amgen/Pfizer) was not effective in ANCA-associated vasculitis
TGFβ	TGFβ-specific antibody that blocks TGFβ1	Renal scarring in diabetic nephropathy	Clinical trials ongoing (NCT01113801*)
TWEAK	TWEAK-specific antibody	Lupus nephritis, lipid nephropathy and crescentic glomerulonephritis	Clinical trial ongoing in lupus nephritis (NCT01499355*)
CCR2	CCR2 antagonist	Diabetic nephropathy, hypertensive nephropathy and crescentic glomerulonephritis	Clinical trial of ongoing in diabetic nephropathy (NCT01447147*)
CCR5	CCR5 antagonist	Immune complex glomerulonephritis and allograft rejection	Unknown
TLR2	TLR2-specific antibody	Acute kidney injury	Clinical trial in delayed-kidney allograft function ongoing (NCT01794663*)
Thymocytes	Anti-thymocyte globulin	Numerous immune disorders	Kidney allograft rejection and graft-versus-host disease
Lymphocytes	Anti-lymphocyte globulin	Numerous immune disorders	Kidney allograft rejection and graft-versus-host disease
CD52 (on mature lymphocytes)	CD52-specific monoclonal antibody	Numerous immune disorders	Clinical trials ongoing in ANCA-associated vasculitis (NCT01405807*)
IL-2R (also known as CD25)	IL-2R-specific antibody	Allograft rejection	Prevention of kidney allograft rejection‡
B7-1 (also known as CD80)	CTLA4–Fc fusion protein	Allograft rejection and lupus nephritis	• Prevention of kidney allograft rejection in a Phase II clinical trial • Negative results from a Phase III clinical trial is under debate and further studies are ongoing (NCT00774852*)
$CD20^+$ B cells	CD20-specific antibody	Lupus nephritis and anti-GBM disease	• Effective in refractory lupus nephritis (uncontrolled studies) • Not effective in LUNAR trial as an add-on to steroids and mycophenolate mofetil • Effective in clinical trials for ANCA-associated vasculitis‡ (RAVE and RITUXVAS trials) • Beneficial in observational studies of membranous nephropathy; controlled clinical trials ongoing (NCT01508468*; NCT01180036*) • Trials ongoing in steroid resistant focal glomerulosclerosis (NCT01573533*; NCT00981838*; NCT00550342*)
BLYS (on B cells)	BLYS-specific antibody	SLE, including lupus nephritis	• Effective in SLE but not specifically for severe lupus nephritis (further trials ongoing) • Clinical trials ongoing in membranous nephropathy (NCT01762852*; NCT01610492*)
BAFF (on B cells)	BAFF-specific antibody	None reported	Effective in SLE and clinical trials ongoing in lupus nephritis (NCT01639339*)
C5	C5-specific antibody or orally active C5aR inhibitor	Anti-MPO FNGN	Effective in atypical HUS, unclear data on effectiveness in STEC-HUS and clinical trials ongoing in ANCA-associated vasculitis (NCT01363388*)

ANCAs, anti-neutrophil cytoplasmic antibodies; BAFF, B cell-activating factor; BLYS, B lymphocyte stimulator; C5, complement component C5; C5aR, C5a anaphylatoxin chemotactic receptor; CCR, CC-chemokine receptor; CTLA4, cytotoxic T lymphocyte antigen 4; FNGN, focal necrotizing glomerulonephritis; GBM, glomerular basement membrane; HUS, haemolytic uraemic syndrome; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; MPO, myeloperoxidase; SLE, systemic lupus erythematosus; STEC-HUS, Shiga toxin-producing *Escherichia coli*-induced haemolytic uraemic syndrome; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; TWEAK, TNF-related weak inducer of apoptosis. *Identifier on ClinicalTrials.gov. ‡Treatment approved by the US Food and Drug Administration.

injury. Unexpectedly, injury is not caused by autoantibodies, as it occurs in B cell-deficient mice[134]. Instead, it is caused by DTH[134], as it can be transferred by T cells[136] and is abrogated in IL-17A-deficient mice[137]. Disease severity is modulated by forkhead box P3 (FOXP3)$^+$ T_{Reg} cells, which are induced by IL-10-producing mast cells that are recruited to regional lymph nodes after immunization with MPO[17].

Neutrophil extracellular traps (NETs) are generated in patients with FNGN[123] and have been suggested to initiate the synthesis of autoantibodies to MPO. This is consistent with the observation that the delivery of NETs to mice — either through direct injection or through adoptive transfer of NET-pulsed DCs[125] — induces autoimmunity to MPO (and to DNA)[125]. However, the administration of PR3 does not provoke pauci-immune FNGN in rodents[120,121].

The stimuli that initiate autoantibody synthesis in pauci-immune FNGN remain unknown but have been linked to infection since the earliest clinical descriptions were made. Recent studies are beginning to suggest why:

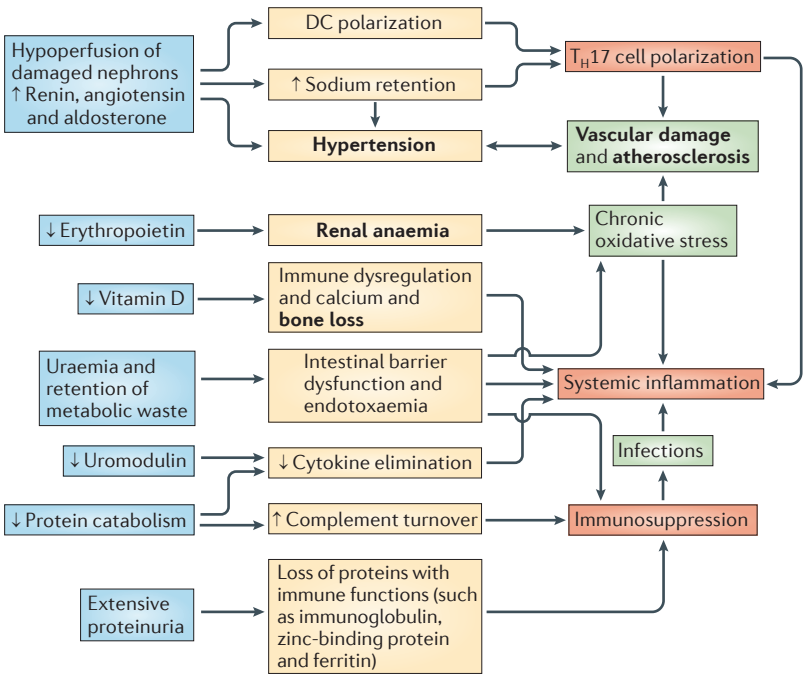


Figure 4 | **Consequences of chronic kidney disease with potential effects on systemic immunity.** Chronic kidney disease (CKD) has several immediate consequences (blue boxes), which are proposed to result in three main immunological alterations (red boxes) through intermediate steps. First, chronic stimulation of the renin–angiotensin–aldosterone system causes T helper 17 (T_H17) cell polarization, through dendritic cell (DC) polarization and possibly through sodium retention. Second, uraemic intestinal barrier dysfunction, vitamin D deficiency and cytokine accumulation (which may be due to impaired protein catabolism, reduced uromodulin levels and chronic oxidative stress) result in systemic inflammation. Third, systemic immunosuppression results from the uraemic accumulation of toxic metabolic waste, the increased turnover of the components of the alternative complement pathway because of impaired protein catabolism, and in cases of extensive proteinuria, the urinary loss of proteins with immunological functions. This figure also integrates the key clinical consequences of CKD, which include hypertension, vascular damage and atherosclerosis, renal anaemia and bone loss (in bold). These mechanisms may alone or in concert affect general immunity.

nasal carriage of *Staphylococcus aureus* is associated with clinical disease relapses[119], and proteins that are derived from this pathogen have been shown to induce B cells from patients with pauci-immune FNGN to produce PR3-specific antibodies[138]. Some patients with autoimmunity to PR3 have been reported to have anti-idiotypic antibodies that bind to a peptide with a sequence that is complementary to PR3 (REF. 130). The complementary peptide is similar to staphylococcal and other microbial proteins, and it has been suggested that these proteins may function as molecular mimics. However, these results have not been confirmed[139]. By contrast, there is strong evidence for molecular mimicry between LAMP2 and the bacterial adhesion protein FimH[120]. Autoantibodies specific for LAMP2 commonly bind to and cross-react with an epitope in FimH. Moreover, immunization of WKY rats with FimH induces the production of antibodies that bind to human and rat LAMP2 and it promotes the development of pauci-immune FNGN. This confirms the molecular mimicry between the two molecules and suggests a pathogenic role for LAMP2-specific autoantibodies. Detailed prospective clinical analyses are now needed to determine the role of the molecular mimicry of LAMP2 in pauci-immune FNGN.

The effect of CKD on systemic immunity

The state of reduced renal function that results from CKD causes marked alterations in the immune system, including persistent systemic inflammation and acquired immunosuppression[140] (FIG. 4). Typical alterations include increased systemic concentrations of pro-inflammatory cytokines and acute phase proteins, such as the pentraxins, as well as dysfunctional phagocytes, B cells and T cells[141]. The persistent systemic inflammation contributes to bone loss, accelerated atherogenesis and body wasting, whereas the immunosuppressed state accounts for infectious complications, which together determine the morbidity and the mortality that is associated with CKD. The immune dysregulation was previously attributed to the effects of haemodialysis but is now known to precede it and to persist afterwards[142]. Several recently discovered consequences of the loss of kidney functions on immune responses are described below, which alone, or in concert, may affect general immunity (FIG. 4).

Uraemia. CKD results in the retention of low-molecular-mass metabolites, such as phenylacetic acid, homocysteine, various sulfates, guanidine compounds and many others. These have inhibitory effects on immune cell activation, promote leukocyte apoptosis and induce the oxidative burst in phagocytes[143]. Chronic oxidative stress increases protein oxidation, which reduces the activity of enzymes, cytokines and antibodies, contributing to both general inflammation and immune dysfunction in CKD. Moreover, oxidized low-density lipoproteins attract and activate granulocytes, and high-density lipoproteins, which are normally anti-atherogenic, are altered to lipoproteins with pro-atherogenic properties[144].

Uraemia affects systemic immunity by causing intestinal dysbiosis and by destabilizing the intestinal barrier[140,145] (FIG. 4). The metabolic consequences of uraemia favour pathogen overgrowth, which can increase the production of uraemic toxins inside the gut and can reduce the production of immunoregulatory short-chain fatty acids[146]. As in heart failure and liver cirrhosis, uraemia-related hypervolaemia leads to intestinal wall congestion, which impairs the intestinal wall barrier and promotes the leakage of pathogen-associated molecular patterns (PAMPs) into the circulation[140]. In fact, systemic lipopolysaccharide (LPS) levels increase in patients with CKD as renal function declines and are highest among those on dialysis[147]. Intestinal PAMP leakage may not only activate innate immune-mediated systemic inflammation but also, paradoxically, could lead to concomitant immunosuppression, through similar mechanisms that account for endotoxin tolerance *in vitro* and compensatory anti-inflammatory syndrome in patients with advanced sepsis[148,149] (FIG. 4).

Renal protein catabolism. Proteins and polypeptides with a molecular mass below 50 kDa pass into the glomerular filtrate and are reabsorbed and catabolized by the tubular epithelium to enable amino acids to be recycled. They consequently accumulate in the blood of patients with CKD, reaching concentrations more than tenfold higher than normal in severe cases, and they have marked effects on immune function[143]. Examples of these effects include the following: an accumulation of IgG light chains (25 kDa in size) suppresses B cell and granulocyte function; increased concentrations of the MHC class I component β2 microglobulin (45 kDa in size) aggregate into amyloid fibrils; increased concentrations of leptin (16 kDa in size) and the granulocyte protein resistin (12 kDa in size) diminish phagocyte function; increased levels of complement factor D (27 kDa in size) enhance the activity of the alternative complement pathway and generate immunosuppressive fragments (such as the complement factor B Ba fragment; which, as a result of its 33 kDa size, also accumulates in CKD on its own[150]); the accumulation of retinol-binding proteins (21 kDa in size) may influence the ratio of T_{Reg} cells to T_H17 cells; and elevated levels of cytokines (typically 10–40 kDa in size) contribute to systemic inflammation (FIG. 4).

In proteinuria, proteins larger than 50 kDa in size are excreted in the urine. The loss of immunoglobulins, complement factors, zinc-binding protein and transferrin contributes to the acquired humoral and cellular immunodeficient state that predisposes patients with nephrotic syndrome to bacterial infections (FIG. 4). Furthermore, several functional T cell and macrophage defects have been described in these patients[143] but their functional relevance is unclear.

Kidney-derived hormones and hypertension. Vitamin D is activated by hydroxylation in the kidneys, and declining levels in CKD lead to renal osteopathy. Vitamin D has immunosuppressive properties and low levels predispose individuals to rheumatic disorders[151]. These disorders are indeed more prevalent in CKD, but it is unclear whether this is because low vitamin D levels are pathogenic or because rheumatic diseases cause CKD, or both. In addition, diseased kidneys cannot produce sufficient quantities of erythropoietin, resulting in the development of renal anaemia, which contributes to oxidative stress that is induced by the accumulation of uraemic toxins[152]; this is especially common when anaemia is treated with iron, which itself causes oxidative stress.

Blood levels of the blood pressure regulator renin are increased in CKD as a result of the hypoperfusion of the damaged nephrons (FIG. 4). DCs express receptors for the downstream mediator of renin, aldosterone, and respond to aldosterone by promoting T_H17 cell polarization[153]. Aldosterone increases sodium reabsorption, and high salt concentrations have recently been shown to maintain T_H17 cell polarization and to aggravate T_H17 cell-driven autoimmunity in mice[154,155]. IL-17 in turn increases blood pressure by promoting vascular inflammation[156]. Sodium retention also causes macrophages to produce vascular endothelial growth factor C (VEGFC), which induces neo-lymphangiogenesis in the skin to store the salt[157]. This in turn increases extracellular volume and, thus, blood pressure. Hypertension generally promotes tissue inflammation, and tubulointerstitial nephritis is known to raise blood pressure[158]. In summary, there are complex feedback loops involving renin–angiotensin–aldosterone stimulation, salt homeostasis, T_H17 cells and mononuclear phagocytes that may exacerbate hypertension and systemic inflammation, and that may promote autoimmunity (FIG. 4). The clinical implications of these interactions warrant further studies.

Concluding remarks

Numerous discoveries have recently been made in the field of renal immunology, which have clarified severe and previously inexplicable kidney diseases; for example, the identification of kidney-specific DAMPs, such as uromodulin, that can drive sterile kidney inflammation, or the identification of autoantigens that are targeted in prevalent forms of glomerulonephritis, such as PLA2R in membranous nephropathy. Knowledge about relevant autoantigens is instrumental for the design of non-invasive diagnostic procedures, such as autoantibody assays. Progress has also been made in understanding why the kidneys are frequent targets of systemic autoimmunity, especially to injury by altered antibodies, immune complexes and complement factors, and this has helped in implementing new treatments in some cases. There are also anatomical and physiological features that render the kidneys susceptible to distinct forms of immune-mediated injury, such as the high osmolarity of the renal medulla, which favours crystal precipitation and inflammasome activation, or the constitutive renal protein catabolism of tubular epithelial cells, which exposes them to T cell effector functions. Cellular immunity seems to require more time to destroy the kidneys than it does to destroy other tissues, making this organ a good site for basic studies on immune cell crosstalk because immune cell infiltrates can be observed over a longer time span.

Endotoxin tolerance
A transient state of hyporesponsiveness of the host or of cultured macrophages and/or monocytes to lipopolysaccharide (LPS) following previous exposure to LPS.

Novel immune mechanisms that have been uncovered during such studies — some of which are discussed in this Review — may be relevant in the context of other organ diseases. The revelation that the kidneys contribute to immune tolerance and that their detoxifying and electrolyte-balancing activities ensure normal immune effector cell function and intestinal microbial homeostasis has been surprising. The kidney is the archetypal organ of homeostasis and it is interesting to see that this role now extends to the immune system.

Despite the progress that has been made, many questions remain unanswered, some of which are highlighted in this Review. Although the mechanisms of kidney disease progression are increasingly well understood, the factors that initiate these diseases often remain unclear, for example, in IgA nephropathy, crescentic glomerulonephritis and membranous nephropathy. However, the development of new therapies from basic discoveries has already begun to affect clinical practise in nephrology (TABLE 1).

1. Kaissling, B. & Le Hir, M. Characterization and distribution of interstitial cell types in the renal cortex of rats. *Kidney Int.* **45**, 709–720 (1994).
2. Kruger, T. *et al.* Identification and functional characterization of dendritic cells in the healthy murine kidney and in experimental glomerulonephritis. *J. Am. Soc. Nephrol.* **15**, 613–621 (2004).
3. Soos, T. J. *et al.* CX3CR1$^+$ interstitial dendritic cells form a contiguous network throughout the entire kidney. *Kidney Int.* **70**, 591–596 (2006).
4. Woltman, A. M. *et al.* Quantification of dendritic cell subsets in human renal tissue under normal and pathological conditions. *Kidney Int.* **71**, 1001–1008 (2007).
5. Guilliams, M. *et al.* From skin dendritic cells to a simplified classification of human and mouse dendritic cell subsets. *Eur. J. Immunol.* **40**, 2089–2094 (2010).
6. Miller, J. C. *et al.* Deciphering the transcriptional network of the dendritic cell lineage. *Nature Immunol.* **13**, 888–899 (2012).
7. Schraml, B. U. *et al.* Genetic tracing via expression history of DNGR-1 defines dendritic cells as a hematopoietic lineage. *Cell* **154**, 843–858 (2013).
8. Tittel, A. P. *et al.* Functionally relevant neutrophilia in CD11c diphtheria toxin receptor transgenic mice. *Nature Methods* **9**, 385–390 (2012).
9. Hochheiser, K. *et al.* Exclusive CX_3CR1-dependence of kidney dendritic cells impacts glomerulonephritis progression. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI70143 (2013).
10. Kim, K. W. *et al. In vivo* structure/function and expression analysis of the CX3C chemokine fractalkine. *Blood* **118**, e156–e167 (2011).
11. Dong, X. *et al.* Resident dendritic cells are the predominant TNF-secreting cell in early renal ischemia-reperfusion injury. *Kidney Int.* **71**, 619–628 (2007).
12. Pindjakova, J. *et al.* Interleukin-1 accounts for intrarenal Th17 cell activation during ureteral obstruction. *Kidney Int.* **81**, 379–390 (2012).
13. Merad, M., Ginhoux, F. & Collin, M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. *Nature Rev. Immunol.* **8**, 935–947 (2008).
14. Nelson, P. J. *et al.* The renal mononuclear phagocytic system. *J. Am. Soc. Nephrol.* **23**, 194–203 (2012).
This paper summarizes the phenotypical range of mononuclear phagocytes in healthy and diseased kidneys.
15. Timoshanko, J. R., Kitching, R., Semple, T. J., Tipping, P. G. & Holdsworth, S. R. A pathogenetic role for mast cells in experimental crescentic glomerulonephritis. *J. Am. Soc. Nephrol.* **17**, 150–159 (2006).
16. Scandiuzzi, L. *et al.* Mouse mast cell protease-4 deteriorates renal function by contributing to inflammation and fibrosis in immune complex-mediated glomerulonephritis. *J. Immunol.* **185**, 624–633 (2010).
17. Gan, P. Y. *et al.* Mast cells contribute to peripheral tolerance and attenuate autoimmune vasculitis. *J. Am. Soc. Nephrol.* **23**, 1955–1966 (2012).
18. Dong, X. *et al.* Antigen presentation by dendritic cells in renal lymph nodes is linked to systemic and local injury to the kidney. *Kidney Int.* **68**, 1096–1108 (2005).
19. Heymann, F. *et al.* Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. *J. Clin. Invest.* **119**, 1286–1297 (2009).
This study shows that T cells can induce glomerular damage and that DC maturation drives glomerulonephritis progression.
20. Lukacs-Kornek, V. *et al.* The kidney-renal lymph node-system contributes to cross-tolerance against innocuous circulating antigen. *J. Immunol.* **180**, 706–715 (2008).
21. Gottschalk, C. *et al.* Batf3-dependent dendritic cells in the renal lymph node induce tolerance against circulating antigens. *J. Am. Soc. Nephrol.* **24**, 543–549 (2013).
22. Bohle, A., Kressel, G., Muller, C. A. & Muller, G. A. The pathogenesis of chronic renal failure. *Pathol. Res. Pract.* **185**, 421–440 (1989).
23. Markovic-Lipkovski, J., Muller, C. A., Risler, T., Bohle, A. & Muller, G. A. Association of glomerular and interstitial mononuclear leukocytes with different forms of glomerulonephritis. *Nephrol. Dial. Transplant.* **5**, 10–17 (1990).
24. Risdon, R. A., Sloper, J. C. & De Wardener, H. E. Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet* **2**, 363–366 (1968).
25. Kriz, W. & LeHir, M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int.* **67**, 404–419 (2005).
26. Bohle, A., Mackensen-Haen, S. & Wehrmann, M. Significance of postglomerular capillaries in the pathogenesis of chronic renal failure. *Kidney Blood Press. Res.* **19**, 191–195 (1996).
27. Floege, J. & Grone, H. J. Progression of renal failure: what is the role of cytokines? *Nephrol. Dial. Transplant.* **10**, 1575–1586 (1995).
28. Abbate, M., Zoja, C. & Remuzzi, G. How does proteinuria cause progressive renal damage? *J. Am. Soc. Nephrol.* **17**, 2974–2984 (2006).
29. Niedermeier, M. *et al.* CD4$^+$ T cells control the differentiation of Gr1$^+$ monocytes into fibrocytes. *Proc. Natl Acad. Sci. USA* **106**, 17892–17897 (2009).
30. Rock, K. L., Latz, E., Ontiveros, F. & Kono, H. The sterile inflammatory response. *Annu. Rev. Immunol.* **28**, 321–342 (2010).
31. Yamanishi, Y. *et al.* TIM1 is an endogenous ligand for LMIR5/CD300b: LMIR5 deficiency ameliorates mouse kidney ischemia/reperfusion injury. *J. Exp. Med.* **207**, 1501–1511 (2010).
32. Anders, H. J. Toll-like receptors and danger signaling in kidney injury. *J. Am. Soc. Nephrol.* **21**, 1270–1274 (2010).
33. Rosin, D. L. & Okusa, M. D. Dangers within: DAMP responses to damage and cell death in kidney disease. *J. Am. Soc. Nephrol.* **22**, 416–425 (2011).
34. Mulay, S. R. *et al.* Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion. *J. Clin. Invest.* **123**, 236–246 (2013).
This paper identifies the role of the NLRP3 inflammasome in crystal nephropathy.
35. Leemans, J. C. *et al.* Renal-associated TLR2 mediates ischemia/reperfusion injury in the kidney. *J. Clin. Invest.* **115**, 2894–2903 (2005).
36. Wu, H. *et al.* TLR4 activation mediates kidney ischemia/reperfusion injury. *J. Clin. Invest.* **117**, 2847–2859 (2007).
37. Allam, R. *et al.* Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. *J. Am. Soc. Nephrol.* **23**, 1375–1388 (2012).
38. McDonald, B. *et al.* Intravascular danger signals guide neutrophils to sites of sterile inflammation. *Science* **330**, 362–366 (2010).
39. Li, L. *et al.* Dendritic cells tolerized with adenosine A_2AR agonist attenuate acute kidney injury. *J. Clin. Invest.* **122**, 3931–3942 (2012).
40. Bonventre, J. V. & Yang, L. Cellular pathophysiology of ischemic acute kidney injury. *J. Clin. Invest.* **121**, 4210–4221 (2011).
41. Zhang, B., Ramesh, G., Uematsu, S., Akira, S. & Reeves, W. B. TLR4 signaling mediates inflammation and tissue injury in nephrotoxicity. *J. Am. Soc. Nephrol.* **19**, 923–932 (2008).
42. Babelova, A. *et al.* Biglycan, a danger signal that activates the NLRP3 inflammasome via toll-like and P2X receptors. *J. Biol. Chem.* **284**, 24035–24048 (2009).
43. Shigeoka, A. A. *et al.* An inflammasome-independent role for epithelial-expressed Nlrp3 in renal ischemia-reperfusion injury. *J. Immunol.* **185**, 6277–6285 (2010).
44. Vilaysane, A. *et al.* The NLRP3 inflammasome promotes renal inflammation and contributes to CKD. *J. Am. Soc. Nephrol.* **21**, 1732–1744 (2010).
45. Wang, W. *et al.* Inflammasome-independent NLRP3 augments TGF-β signaling in kidney epithelium. *J. Immunol.* **190**, 1239–1249 (2013).
This paper shows that NLRP3 and the adaptor protein ASC are needed for TGFβR1 signalling, which might contribute to kidney fibrosis.
46. Eddy, A. A. Scraping fibrosis: UMODulating renal fibrosis. *Nature Med.* **17**, 553–555 (2011).
47. Saemann, M. D. *et al.* Tamm-Horsfall glycoprotein links innate immune cell activation with adaptive immunity via a Toll-like receptor-4-dependent mechanism. *J. Clin. Invest.* **115**, 468–475 (2005).
48. Darisipudi, M. N. *et al.* Uromodulin triggers IL-1β-dependent innate immunity via the NLRP3 Inflammasome. *J. Am. Soc. Nephrol.* **23**, 1783–1789 (2012).
49. Sethi, S. & Fervenza, F. C. Membranoproliferative glomerulonephritis — a new look at an old entity. *N. Engl. J. Med.* **366**, 1119–1131 (2012).
50. Fakhouri, F., Fremeaux-Bacchi, V., Noel, L. H., Cook, H. T. & Pickering, M. C. C3 glomerulopathy: a new classification. *Nature Rev. Nephrol.* **6**, 494–499 (2010).
51. Chen, Q. *et al.* Combined C3b and factor B autoantibodies and MPGN type II. *N. Engl. J. Med.* **365**, 2340–2342 (2011).
52. Martinez-Barricarte, R. *et al.* Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. *J. Clin. Invest.* **120**, 3702–3712 (2010).
53. Gale, D. P. *et al.* Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. *Lancet* **376**, 794–801 (2010).
54. Bomback, A. S. & Appel, G. B. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. *Nature Rev. Nephrol.* **8**, 634–642 (2012).
55. Vivarelli, M., Pasini, A. & Emma, F. Eculizumab for the treatment of dense-deposit disease. *N. Engl. J. Med.* **366**, 1163–1165 (2012).
56. Daina, E., Noris, M. & Remuzzi, G. Eculizumab in a patient with dense-deposit disease. *N. Engl. J. Med.* **366**, 1161–1163 (2012).
57. Trachtman, H., Austin, C., Lewinski, M. & Stahl, R. A. Renal and neurological involvement in typical Shiga toxin-associated HUS. *Nature Rev. Nephrol.* **8**, 658–669 (2012).
58. Morigi, M. *et al.* Alternative pathway activation of complement by Shiga toxin promotes exuberant C3a formation that triggers microvascular thrombosis. *J. Immunol.* **187**, 172–180 (2011).
59. Thurman, J. M. *et al.* Alternative pathway of complement in children with diarrhea-associated hemolytic uremic syndrome. *Clin. J. Am. Soc. Nephrol.* **4**, 1920–1924 (2009).
60. Lapeyraque, A. L. *et al.* Eculizumab in severe Shiga-toxin-associated HUS. *N. Engl. J. Med.* **364**, 2561–2563 (2011).

61. Noris, M., Mescia, F. & Remuzzi, G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nature Rev. Nephrol.* **8**, 622–633 (2012).
62. Legendre, C. M. *et al.* Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N. Engl. J. Med.* **368**, 2169–2181 (2013).
This is a groundbreaking study showing that terminal complement inhibition (using eculizumab) abolishes complement-mediated thrombotic microangiopathy and results in a time-dependent improvement in renal function in patients with aHUS.
63. Furlan, M. *et al.* von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N. Engl. J. Med.* **339**, 1578–1584 (1998).
64. Schreiber, A. *et al.* C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J. Am. Soc. Nephrol.* **20**, 289–298 (2009).
65. Dixon, F. J. What are sensitized cells doing in glomerulonephritis? *N. Engl. J. Med.* **283**, 536–537 (1970).
66. Couser, W. G. Sensitized cells come of age: a new era in renal immunology with important therapeutic implications. *J. Am. Soc. Nephrol.* **10**, 664–665 (1999).
67. Bolton, W. K. What sensitized cells just might be doing in glomerulonephritis. *J. Clin. Invest.* **109**, 713–714 (2002).
68. Sung, S. S. & Bolton, W. K. T cells and dendritic cells in glomerular disease: the new glomerulotubular feedback loop. *Kidney Int.* **77**, 393–399 (2010).
69. Tipping, P. G. & Holdsworth, S. R. T cells in crescentic glomerulonephritis. *J. Am. Soc. Nephrol.* **17**, 1253–1263 (2006).
70. Turner, J. E. *et al.* IL-17A production by renal γδ T cells promotes kidney injury in crescentic GN. *J. Am. Soc. Nephrol.* **23**, 1486–1495 (2012).
71. Summers, S. A. *et al.* Th1 and Th17 cells induce proliferative glomerulonephritis. *J. Am. Soc. Nephrol.* **20**, 2518–2524 (2009).
72. Paust, H. J. *et al.* The IL-23/Th17 axis contributes to renal injury in experimental glomerulonephritis. *J. Am. Soc. Nephrol.* **20**, 969–979 (2009).
73. Turner, J. E. *et al.* CCR6 recruits regulatory T cells and Th17 cells to the kidney in glomerulonephritis. *J. Am. Soc. Nephrol.* **21**, 974–985 (2010).
74. Steinmetz, O. M. *et al.* The Th17-defining transcription factor RORγt promotes glomerulonephritis. *J. Am. Soc. Nephrol.* **22**, 472–483 (2011).
75. Riedel, J. H. *et al.* Immature renal dendritic cells recruit regulatory CXCR6$^+$ invariant natural killer T cells to attenuate crescentic GN. *J. Am. Soc. Nephrol.* **23**, 1987–2000 (2012).
This paper is one of the first descriptions of regulatory iNKT cells having an anti-inflammatory effect. It shows that immature renal DCs attract these cells via the CXCL16–CXCR6 axis to attenuate crescentic glomerulonephritis.
76. Panzer, U. *et al.* Chemokine receptor CXCR3 mediates T cell recruitment and tissue injury in nephrotoxic nephritis in mice. *J. Am. Soc. Nephrol.* **18**, 2071–2084 (2007).
77. Menke, J. *et al.* CXCL9, but not CXCL10, promotes CXCR3-dependent immune-mediated kidney disease. *J. Am. Soc. Nephrol.* **19**, 1177–1189 (2008).
78. Chavele, K. M. *et al.* Mannose receptor interacts with Fc receptors and is critical for the development of crescentic glomerulonephritis in mice. *J. Clin. Invest.* **120**, 1469–1478 (2010).
79. Wolf, D. *et al.* CD4$^+$CD25$^+$ regulatory T cells inhibit experimental anti-glomerular basement membrane glomerulonephritis in mice. *J. Am. Soc. Nephrol.* **16**, 1360–1370 (2005).
This is the first study to describe a role for T_{Reg} cells in kidney disease.
80. Paust, H. J. *et al.* Regulatory T cells control the Th1 immune response in murine crescentic glomerulonephritis. *Kidney Int.* **80**, 154–164 (2011).
81. Ooi, J. D. *et al.* Endogenous foxp3$^+$ T-regulatory cells suppress anti-glomerular basement membrane nephritis. *Kidney Int.* **79**, 977–986 (2011).
82. Hochheiser, K. *et al.* Kidney dendritic cells become pathogenic during crescentic glomerulonephritis with proteinuria. *J. Am. Soc. Nephrol.* **22**, 306–316 (2011).
83. Feng, L. *et al.* Prevention of crescentic glomerulonephritis by immunoneutralization of the fractalkine receptor CX_3CR1 rapid communication. *Kidney Int.* **56**, 612–620 (1999).
84. Goldwich, A. *et al.* Podocytes are nonhematopoietic professional antigen-presenting cells. *J. Am. Soc. Nephrol.* **24**, 906–916 (2013).
85. Li, S., Kurts, C., Kontgen, F., Holdsworth, S. R. & Tipping, P. G. Major histocompatibility complex class II expression by intrinsic renal cells is required for crescentic glomerulonephritis. *J. Exp. Med.* **188**, 597–602 (1998).
86. Ryu, M. *et al.* Plasma leakage through glomerular basement membrane ruptures triggers the proliferation of parietal epithelial cells and crescent formation in non-inflammatory glomerular injury. *J. Pathol.* **228**, 448–494 (2012).
87. Neale, T. J., Tipping, P. G., Carson, S. D. & Holdsworth, S. R. Participation of cell-mediated immunity in deposition of fibrin in glomerulonephritis. *Lancet* **2**, 421–424 (1988).
88. Zaferani, A. *et al.* Identification of tubular heparan sulfate as a docking platform for the alternative complement component properdin in proteinuric renal disease. *J. Biol. Chem.* **286**, 5359–5367 (2011).
89. Macconi, D. *et al.* Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. *J. Am. Soc. Nephrol.* **20**, 123–130 (2009).
90. Ooi, J. D., Holdsworth, S. R. & Kitching, A. R. Advances in the pathogenesis of Goodpasture's disease: From epitopes to autoantibodies to effector T cells. *J. Autoimmun.* **31**, 295–300 (2008).
91. Reynolds, J. Strain differences and the genetic basis of experimental autoimmune anti-glomerular basement membrane glomerulonephritis. *Int. J. Exp. Pathol.* **92**, 211–217 (2011).
92. Pedchenko, V. *et al.* Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. *N. Engl. J. Med.* **363**, 343–354 (2010).
This paper clarifies the crucial importance of autoantigen conformation for autoantibody binding in anti-GBM disease.
93. Olaru, F. *et al.* Proteolysis breaks tolerance toward intact α345(IV) collagen, eliciting novel anti-glomerular basement membrane autoantibodies specific for α345NC1 hexamers. *J. Immunol.* **190**, 1424–1432 (2013).
94. Phelps, R. G. & Rees, A. J. The HLA complex in Goodpasture's disease: A model for analyzing susceptibility to autoimmunity. *Kidney Int.* **56**, 1638–1653 (1999).
95. Cairns, L. S. *et al.* The fine specificity and cytokine profile of T-helper cells responsive to the α3 chain of type IV collagen in Goodpasture˜s disease. *J. Am. Soc. Nephrol.* **14**, 2801–2812 (2003).
96. Zou, J. *et al.* Healthy individuals have Goodpasture autoantigen-reactive T cells. *J. Am. Soc. Nephrol.* **19**, 396–404 (2008).
97. Ooi, J. D. *et al.* The HLA-DRB1*15: 01-restricted Goodpasture's T cell epitope induces GN. *J. Am. Soc. Nephrol.* **24**, 419–431 (2013).
This study shows the crucial role of HLA-DR*15:01 in the autoimmune response to the α3(IV)NC1, which is the target of autoimmunity in anti-GBM disease.
98. Phelps, R. G., Jones, V. L., Coughlan, M., Turner, A. N. & Rees, A. J. Presentation of the Goodpasture autoantigen to CD4 T cells Is influenced more by processing constraints than by HLA class II peptide binding preferences. *J. Biol. Chem.* **273**, 11440–11447 (1998).
99. Kerjaschki, D. & Farquhar, M. G. Immunocytochemical localization of the Heymann nephritis antigen (GP330) in glomerular epithelial cells of normal Lewis rats. *J. Exp. Med.* **157**, 667–686 (1983).
100. Beck, L. H. Jr *et al.* M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N. Engl. J. Med.* **361**, 11–21 (2009).
This seminal paper identifies PLA2R as the enigmatic autoantigen in membranous nephropathy.
101. Stahl, R., Hoxha, E. & Fechner, K. PLA2R autoantibodies and recurrent membranous nephropathy after transplantation. *N. Engl. J. Med.* **363**, 496–498 (2010).
102. Stanescu, H. C. *et al.* Risk HLA-DQA1 and PLA_2R1 alleles in idiopathic membranous nephropathy. *N. Engl. J. Med.* **364**, 616–626 (2011).
103. Suzuki, H. *et al.* IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. *J. Clin. Invest.* **118**, 629–639 (2008).
104. Suzuki, H. *et al.* Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. *J. Clin. Invest.* **119**, 1668–1677 (2009).
This is a seminal paper indicating that glycan-specific autoantibodies are associated with IgA nephropathy and may represent a disease-specific marker and potential therapeutic target.
105. Berthoux, F. *et al.* Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J. Am. Soc. Nephrol.* **23**, 1579–1587 (2012).
106. Goodnow, C. C. Multistep pathogenesis of autoimmune disease. *Cell* **130**, 25–35 (2007).
107. Hakkim, A. *et al.* Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc. Natl Acad. Sci. USA* **107**, 9813–9818 (2010).
108. Bosch, X. Systemic lupus erythematosus and the neutrophil. *N. Engl. J. Med.* **365**, 758–760 (2011).
109. Marshak-Rothstein, A. & Rifkin, I. R. Immunologically active autoantigens: the role of toll-like receptors in the development of chronic inflammatory disease. *Annu. Rev. Immunol.* **25**, 419–441 (2007).
110. Guiducci, C. *et al.* TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature* **465**, 937–941 (2010).
This study shows that TLR7 and TLR9 signalling drives lupus nephritis by rendering DCs resistant to steroids.
111. Pawar, R. D. *et al.* Inhibition of Toll-like receptor-7 (TLR-7) or TLR-7 plus TLR-9 attenuates glomerulonephritis and lung injury in experimental lupus. *J. Am. Soc. Nephrol.* **18**, 1721–1731 (2007).
112. Savarese, E. *et al.* U1 small nuclear ribonucleoprotein immune complexes induce type I interferon in plasmacytoid dendritic cells through TLR7. *Blood* **107**, 3229–3234 (2006).
113. Garcia-Romo, G. S. *et al.* Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci. Transl. Med.* **3**, 73ra20 (2011).
114. Theofilopoulos, A. N., Baccala, R., Beutler, B. & Kono, D. H. Type I interferons (α/β) in immunity and autoimmunity. *Annu. Rev. Immunol.* **23**, 307–336 (2005).
115. Migliorini, A. & Anders, H. J. A novel pathogenetic concept-antiviral immunity in lupus nephritis. *Nature Rev. Nephrology* **8**, 183–189 (2012).
116. Yung, S., Cheung, K. F., Zhang, Q. & Chan, T. M. Anti-dsDNA antibodies bind to mesangial annexin II in lupus nephritis. *J. Am. Soc. Nephrol.* **21**, 1912–1927 (2010).
117. Mortensen, E. S. & Rekvig, O. P. Nephritogenic potential of anti-DNA antibodies against necrotic nucleosomes. *J. Am. Soc. Nephrol.* **20**, 696–704 (2009).
118. Weening, J. J. *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J. Am. Soc. Nephrol.* **15**, 241–250 (2004).
119. Chen, M. & Kallenberg, C. G. ANCA-associated vasculitides — advances in pathogenesis and treatment. *Nature Rev. Rheumatol* **6**, 653–664 (2010).
120. Kain, R. *et al.* Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. *Nature Med.* **14**, 1088–1096 (2008).
This paper describes molecular mimicry of bacterial antigens underlying pauci-immune FNGN.
121. Kain, R. *et al.* High prevalence of autoantibodies to hLAMP-2 in anti-neutrophil cytoplasmic antibody-associated vasculitis. *J. Am. Soc. Nephrol.* **23**, 556–566 (2012).
122. Roth, A. J. *et al.* Anti-LAMP-2 antibodies are not prevalent in patients with antineutrophil cytoplasmic autoantibody glomerulonephritis. *J. Am. Soc. Nephrol.* **23**, 545–555 (2012).
123. Kessenbrock, K. *et al.* Netting neutrophils in autoimmune small-vessel vasculitis. *Nature Med.* **15**, 623–625 (2009).
124. Gou, S.-J., Yuan, J., Chen, M., Yu, F. & Zhao, M.-H. Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int.* **83**, 129–137 (2013).
125. Schreiber, A. & Kettritz, R. The neutrophil in antineutrophil cytoplasmic autoantibody-associated vasculitis. *J. Leukoc. Biol.* http://dx.doi.org/10.1189/jlb.1012525 (2013).
126. Abdulahad, W. H., Lamprecht, P. & Kallenberg, C. G. T-helper cells as new players in ANCA-associated vasculitides. *Arthritis Res. Ther.* **13**, 236 (2011).

127. Velden, J. *et al.* Renal IL-17 expression in human ANCA-associated glomerulonephritis. *Am. J. Physiol. Renal Physiol.* **302**, F1663–F1673 (2012).
128. McKinney, E. F. *et al.* A $CD8^+$ T cell transcription signature predicts prognosis in autoimmune disease. *Nature Med.* **16**, 586–591 (2010).
129. Lyons, P. A. *et al.* Genetically distinct subsets within ANCA-associated vasculitis. *N. Engl. J. Med.* **367**, 214–223 (2012).
130. Jennette, J. C., Falk, R. J., Hu, P. & Xiao, H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. *Annu. Rev. Pathol.* **8**, 139–160 (2013).
131. Heeringa, P. & Little, M. A. *In vivo* approaches to investigate ANCA-associated vasculitis: lessons and limitations. *Arthritis Res. Ther.* **13**, 204 (2011).
132. Kuligowski, M. P. *et al.* Antimyeloperoxidase antibodies rapidly induce α4-integrin-dependent glomerular neutrophil adhesion. *Blood* **113**, 6485–6494 (2009).
133. Little, M. A. *et al.* Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. *PLoS ONE* **7**, e28626 (2012).
134. Ruth, A. J. *et al.* Anti-neutrophil cytoplasmic antibodies and effector $CD4^+$ cells play nonredundant roles in anti-myeloperoxidase crescentic glomerulonephritis. *J. Am. Soc. Nephrol.* **17**, 1940–1949 (2006).
135. Tan, D. S. *et al.* Thymic deletion and regulatory T cells prevent antimyeloperoxidase GN. *J. Am. Soc. Nephrol.* **24**, 573–585 (2013).
136. Ooi, J. D. *et al.* The immunodominant myeloperoxidase T-cell epitope induces local cell-mediated injury in antimyeloperoxidase glomerulonephritis. *Proc. Natl Acad. Sci. USA* **109**, E2615–E2624 (2012).
137. Gan, P. Y. *et al.* Th17 cells promote autoimmune anti-myeloperoxidase glomerulonephritis. *J. Am. Soc. Nephrol.* **21**, 925–931 (2010).
138. Tadema, H. *et al.* Bacterial DNA motifs trigger ANCA production in ANCA-associated vasculitis in remission. *Rheumatology (Oxford)* **50**, 689–696 (2011).
139. Tadema, H., Kallenberg, C. G., Stegeman, C. A. & Heeringa, P. Reactivity against complementary proteinase-3 is not increased in patients with PR3-ANCA-associated vasculitis. *PLoS ONE* **6**, e17972 (2011).
140. Vaziri, N. D. CKD impairs barrier function and alters microbial flora of the intestine: a major link to inflammation and uremic toxicity. *Curr. Opin. Nephrol. Hypertens.* **21**, 587–592 (2012).
141. Lech, M., Rommele, C. & Anders, H. J. Pentraxins in nephrology: C-reactive protein, serum amyloid P and pentraxin-3. *Nephrol. Dial. Transplant.* **28**, 803–811 (2013).
142. Carrero, J. J. & Stenvinkel, P. Inflammation in end-stage renal disease — what have we learned in 10 years? *Semin. Dial.* **23**, 498–509 (2010).
143. Cohen, G. & Horl, W. H. Immune dysfunction in uremia — an update. *Toxins* **4**, 962–990 (2012).
144. Weichhart, T. *et al.* Serum amyloid A in uremic HDL promotes inflammation. *J. Am. Soc. Nephrol.* **23**, 934–947 (2012).
145. Anders, H. J., Andersen, K. & Stecher, B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int.* **83**, 1010–1016 (2013).
146. Meyer, T. W. & Hostetter, T. H. Uremic solutes from colon microbes. *Kidney Int.* **81**, 949–954 (2012).
147. McIntyre, C. W. *et al.* Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* **6**, 133–141 (2011).
148. Hotchkiss, R. S., Coopersmith, C. M., McDunn, J. E. & Ferguson, T. A. The sepsis seesaw: tilting toward immunosuppression. *Nature Med.* **15**, 496–497 (2009).
149. Stearns-Kurosawa, D. J., Osuchowski, M. F., Valentine, C., Kurosawa, S. & Remick, D. G. The pathogenesis of sepsis. *Annu. Rev. Pathol.* **6**, 19–48 (2011).
150. Oppermann, M. *et al.* Elevated plasma levels of the immunosuppressive complement fragment Ba in renal failure. *Kidney Int.* **40**, 939–947 (1991).
151. Pelajo, C. F., Lopez-Benitez, J. M. & Miller, L. C. Vitamin D and autoimmune rheumatologic disorders. *Autoimmun Rev.* **9**, 507–510 (2010).
152. Vaziri, N. D. Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin. Nephrol.* **24**, 469–473 (2004).
153. Herrada, A. A. *et al.* Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity. *J. Immunol.* **184**, 191–202 (2010).
154. Kleinewietfeld, M. *et al.* Sodium chloride drives autoimmune disease by the induction of pathogenic T_H17 cells. *Nature* **496**, 518–522 (2013).
155. Wu, C. *et al.* Induction of pathogenic T_H17 cells by inducible salt-sensing kinase SGK1. *Nature* **496**, 513–517 (2013).
156. Madhur, M. S. *et al.* Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension* **55**, 500–507 (2010).
157. Machnik, A. *et al.* Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nature Med.* **15**, 545–552 (2009).
158. Harrison, D. G., Marvar, P. J. & Titze, J. M. Vascular inflammatory cells in hypertension. *Front. Physiol.* **3**, 128 (2012).

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