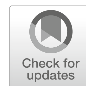
Chapter 8
Inflammasomes in the Kidney



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M. D. Cordero, E. Alcocer-Gómez (eds.), *Inflammasomes: Clinical and Therapeutic Implications*, Experientia Supplementum 108,
https://doi.org/10.1007/978-3-319-89390-7_8

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Abstract Inflammasomes influence a diverse range of kidney disease, including acute and chronic kidney diseases, and those mediated by innate and adaptive immunity. Both IL-18 and in particular IL-1β are validated therapeutic targets in several kidney diseases. In addition to leukocyte-derived inflammasomes, renal tissue cells express functional inflammasome components. Furthermore, a range of endogenous substances that directly activate inflammasomes also mediate kidney injury. Many of the functional studies have focussed on the NLRP3 inflammasome, and there is also evidence for the involvement of other inflammasomes in some conditions. While, at least in some disease, the mechanistic details of the involvement of the inflammasome remain to be elucidated, therapies focussed on inflammasomes and their products have potential in treating kidney disease in the future.

Keywords Inflammasome · Glomerulonephritis · Acute kidney injury · Diabetic nephropathy · Interleukin-1β

The kidney is prone to injury from a range of metabolic, toxic and immunologic insults. The NLRP3 inflammasome is present in kidney tissue cells as well as immune cells within the kidney (such as infiltrating and resident mononuclear phagocytes) and has been implicated in the pathogenesis of a broad spectrum of kidney diseases. Cellular stress caused by an ischaemic, septic or nephrotoxic insult, or by albuminuria itself, provokes the release of NLRP3 inflammasome-activating 'danger signals', or damage-associated molecular proteins (DAMPs) from cells (Akcay et al. 2009; Liu et al. 2014). Other substances associated with kidney injury, such as cholesterol emboli (Duewell et al. 2010) and monosodium urate (Martinon et al. 2006), can themselves act as a signal for NLRP3-ASC oligomerisation and inflammasome formation. After activation, the NLRP3 inflammasome promotes kidney injury via pro-inflammatory cytokines and may also switch on fibrotic (Vilaysane et al. 2010) and cell death pathways (Shen et al. 2016). Thus, the NLRP3 inflammasome may be a mechanistic link between processes that have long been known to cause kidney injury and the injurious inflammatory response that follows. Inhibition of the NLRP3 inflammasome is protective in several models of glomerular and tubulointerstitial kidney disease, indicating its potential for treatment of human disease.

The role of inflammasomes other than NLRP3 in the kidney is less well defined. The AIM2 inflammasome, activated by double-stranded DNA (Fernandes-Alnemri et al. 2009), has been shown to have a potential role in hepatitis B-related glomerulonephritis (Du et al. 2013; Zhen et al. 2014) and in experimental lupus (Choubey and

Panchanathan 2017), although it has not been directly linked to lupus nephritis. The NLRC4 inflammasome is important in pathogenic IL-1β production in a mouse model of diabetes mellitus (Yuan et al. 2016). Although bacterial infection has been linked to some types of glomerulonephritis and is the trigger for the NLRP1 and NLRC4 inflammasomes, few studies have focussed on a role for these inflammasomes in autoimmune kidney disease (Man and Kanneganti 2015).

8.1 Basic Renal Structure and Function

The primary role of the kidney is to filter blood, maintaining levels of electrolytes such as sodium and potassium and excreting nitrogenous wastes such as urea, excess body water and electrolytes into the urine. The functional unit of a kidney a nephron, comprised of a glomerulus, a specialised filter through which blood passes from an afferent arteriole into capillaries that have evolved to generate an ultrafiltrate that accumulates in the urinary (Bowman's) space, and a tubule, through which the glomerular filtrate passes from the urinary space, with reabsorption of most of the water and solutes, before being excreted as urine. In healthy humans, kidneys contain on average approximately 900,000 nephrons, although this number varies depending on the ethnicity of the population studied and factors associated with the fetomaternal environment, which influences kidney development (Puelles et al. 2016). Kidneys consist of an outer cortex, inner medulla and renal pelvis. Nephrons traverse the kidney so that the cortex contains the glomeruli and the medulla contains tubules formed into pyramids, which facilitate the reabsorption and excretion of water and electrolytes and the formation of concentrated urine. The apex of pyramids is comprised of collecting tubules, which drain into calyces that in turn drain into the renal pelvis and ureter for excretion.

The structure of the glomerulus allows fluid and small solutes to pass from the bloodstream through the filtration barrier into the urinary space, but large molecules, including plasma proteins, are largely retained within the microvasculature. The glomerular tuft is a network of glomerular capillaries, lying on a scaffold of mesangial cells and extracellular matrix. The glomerular filtration barrier, functioning as a charge and size selective molecular sieve, is composed of three layers: endothelial cells, glomerular basement membrane (GBM) and podocytes (Haraldsson and Jeansson 2009). Glomerular capillaries are on one side of the glomerular filtration barrier with the urinary space (Bowman's space) on the adjacent side. Glomerular endothelial cells line the capillary lumen and contain fenestrae, small transcellular 'holes' covered with endothelial glycocalyx, which aid filtration. The glomerular basement membrane is composed of extracellular matrix macromolecules including type IV collagen, laminin and proteoglycans. Podocytes line the GBM on the side of the urinary space. They are highly specialised epithelial cells with long, interdigitating foot processes that wrap around the glomerular capillaries (Brinkkoetter et al. 2013). Damage to any layer of the glomerular filtration barrier results in a leak of proteins into the urinary space, and proteinuria is thus regarded as one of the hallmarks of glomerular disease. Kidney diseases may be seen as primarily due to pathology of an intrinsic kidney cell, i.e. mesangial cells as the

target of immunologic injury in IgA nephropathy (Tsai et al. 2017), or primarily due to activation or infiltration of immune cells, such as neutrophils in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (Falk et al. 1990). However, the extensive cross talk between different types of cells in the kidney, including intrinsic kidney cells and leukocytes, means that damage to one cell type usually has effects on multiple different cells (Kitching and Hutton 2016). A summary of the function of glomerular cells and some common kidney diseases linked to dysfunction of each cell type is shown in Table 8.1.

Table 8.1 Key functions and responses of intrinsic glomerular cells

Renal cell type	Normal function and features	Responses to injury	Examples of relevant diseases	NLRP3 inflammasome present
Mesangial cells	Maintain structural architecture of glomerulus Mesangial matrix homeostasis Regulate filtration surface area Phagocytose apoptotic cells	Lysis with healthy remodelling Apoptosis Hypertrophy Proliferation and matrix expansion leading to glomerulosclerosis	IgA nephropathy Diabetic nephropathy	Likely
Glomerular endothelial cells	Fenestrations and glycocalyx facilitate selective permeability and filtration	Apoptosis Loss of fenestrations Widening of cell-cell junctions, transcellular holes Glycocalyx damage; loss of GAG synthesis	ANCA-associated glomerulonephritis Lupus nephritis (classes III and IV) Haemolytic-uremic syndrome Diabetic nephropathy	Likely
Podocytes	Foot processes wrap around capillaries Adherence to GBM	Apoptosis Foot process effacement Detachment from GBM; podocyte loss	Minimal change disease Focal and segmental glomerulosclerosis Diabetic nephropathy	Likely
Parietal epithelial cells	Line Bowman's capsule Several subsets of cells likely with different functions	Apoptosis Migration to glomerular tuft, production ECM proteins leading to glomerulosclerosis Proliferation leading to crescent and pseudocrescent formation	Crescentic glomerulonephritis Focal and segmental glomerulosclerosis	Unknown

Adapted from Kitching and Hutton (2016)
ANCA anti-neutrophil cytoplasmic antibody, *GAG* glycosaminoglycan, *GBM* glomerular basement membrane

8.2 NLRP3 Inflammasome Activation in the Kidney

The NLRP3 inflammasome has primarily been described in myeloid cells, particularly macrophages and dendritic cells (Martinon et al. 2009) but also neutrophils (Chen et al. 2016). In inflammatory kidney diseases, leukocyte retention within glomeruli occurs via specialised adhesion molecules. Immune cells may be involved in local tissue inflammation or repair or may influence systemic adaptive immunity which is a key driver of many glomerular diseases (Kitching and Hutton 2016). The presence of the NLRP3 inflammasome in murine kidney tissue cells has been demonstrated in several different studies, generally by showing that these cells can produce IL-1β and IL-18 or by demonstrating co-localisation of inflammasome components such as NLRP3 with ASC and/or caspase-1 in kidney biopsies. Tubular epithelial cells, in both mouse and human, express components for NLRP3 inflammasome complex and produce active IL-1β and/or IL-18 (Faust et al. 2002; Homsi et al. 2006; Lichtnekert et al. 2011; Wang et al. 2015a). While an early murine in vitro study cast doubt on the presence of the inflammasome in glomerular endothelial cells, mesangial cells and podocytes (Lichtnekert et al. 2011), subsequent studies have shown varying levels of evidence of inflammasome activation in these cells (Abais et al. 2013; Shahzad et al. 2015; Zhang et al. 2012; Zhou et al. 2010). Human kidney biopsy studies have documented the presence of the inflammasome in podocytes, mesangial cells, tubular epithelium and intercalated cells (Chun et al. 2016; Gauer et al. 2007; Shahzad et al. 2015). Selected studies documenting the presence of the NLRP3 inflammasome in mouse and human intrinsic glomerular cells are presented in Table 8.2. However, these data should be interpreted with caution, as the presence of ASC and NLRP3 mRNA or co-localisation of NLRP3 with ASC/caspase-1 is not in itself robust evidence for inflammasome activation. Furthermore, ELISAs fail to differentiate between active, cleaved IL-1β or IL-18 and their pro-cytokine forms. Currently, the 'gold standard' readout for inflammasome activation, Western blotting of activated caspase-1, IL-1β or IL-18, can be technically difficult and may not reflect organ specificity (Ludwig-Portugall et al. 2016). The presence of the NLRP3 inflammasome in intrinsic kidney cells is thus still an area of some debate. It may be that NLRP3 inflammasome expression occurs constitutively in tubular cells, but not in other kidney cells, unless switched on during specific diseases in a particular cell type. A study that compared expression of NLRP3 in normal human kidneys, obtained from nephrectomies, and biopsy samples of patients with IgA nephropathy supports this theory, showing the presence of inflammasome components in tubular cells of both groups and in glomerular mesangial cells in patients with IgA nephropathy but not in healthy kidneys (Chun et al. 2016).

Some authors have viewed the data showing the presence of the NLRP3 inflammasome components in renal cells as being evidence that renal cell-derived, rather than immune cell-derived, NLRP3 inflammasome activation is the key driver of pathology in kidney diseases (Chun et al. 2016). Although this may be the case, it can be difficult to interpret the relative contributions of inflammasome activation in

Table 8.2 Selected studies showing evidence for inflammasome activation in intrinsic kidney cells

Disease	Cells involved	Evidence of inflammasome activation	References
Hyperhomocysteinaemia	Podocytes (cultured)	RT-PCR showed NLRP3, ASC and caspase-1 mRNA in cultured podocytes Size exclusion chromatography determined the presence of ASC-NLRP3 complexes in podocyte cultures Co-localisation of NLRP3 with ASC or caspase-1 in podocytes using confocal microscopy and immunofluorescence Small amounts of IL-1β from podocyte cultures by ELISA (not differentiating active from pro-IL-1β)	Zhang et al. (2012)
Primary glomerular diseases	Podocytes (human)	NLRP3 and caspase-1 co-localisation in kidney biopsy of subjects with glomerular disease significantly increased compared to controls. Caspase-1 co-localised with podocyte marker synaptopodin	Xiong et al. (2015)
Lupus nephritis (MRL-Fas^{lpr} mice)	TEC (mouse)	IL-18 detected in sera and kidney tissues by ELISA, RT-PCR and Western blotting. IL-18 production by primary TECs, detected by RT-PCR, ELISA and Western blotting	Faust et al. (2002)
Glycerol-induced AKI	TEC (mouse)	IHC for IL-1β and IL-18 on kidney biopsies localised these to tubules, Western blot on kidney homogenate to determine active IL-1β and IL-18	Homsi et al. (2006)
IgA nephropathy	TEC (but not glomerular cells) in healthy human kidneys. TEC and mesangial cells in IgA nephropathy	Healthy human kidneys stained with immunoperoxidase or processed for indirect IF and confocal microscopy. NLRP3 localised primarily to tubules with absent glomerular staining In vitro NLRP3 present in human proximal tubular cell but not podocyte culture	Chun et al. (2016)
Healthy human kidney	Tubular epithelium	IL-18 mRNA and protein detected by PCR, in situ hybridization and Western blotting in normal human kidneys. IHC located IL-18 to nephron segments of the distal convoluted tubule and to parts of the collecting duct. Confocal microscopy for IL-18 was expressed in intercalated cells	Gauer et al. (2007)

(continued)

Table 8.2 (continued)

Disease	Cells involved	Evidence of inflammasome activation	References
IgA nephropathy	Mouse TEC and mesangial cell cultures	Immune complexes induced secretion of IL-1β in cultured TEC and mesangial cells; IL-1β produced was much reduced in NLRP3-deficient TEC and mesangial cells	Tsai et al. (2017)
Diabetic nephropathy	Mesangial cells (subject to high glucose or LPS)	IL-1β, caspase-1 and NLRP3 mRNA and protein detected in cultured mesangial cells by RT-PCR and immunoblot	Feng et al. (2016)
Diabetes	Endothelial cells and podocytes (mouse and human)	Active IL-1β from murine primary podocyte cultures detected using ELISA. Partial co-localisation of NLRP3 or cleaved caspase-1 with podocytes and glomerular endothelial cells in histological sections of diabetic humans or mice	Shahzad et al. (2015)

ELISA enzyme-linked immunosorbent assay, *RT-PCR* reverse transcription–polymerase chain reaction, *IHC* immunohistochemistry, *TEC* tubular epithelial cells

intrinsic renal cells and immune cells in disease models. For example, one study inhibited ASC in a kidney-restricted fashion, delivering siRNA via the renal artery, and showed improvements in proteinuria and glomerular sclerosis (Zhang et al. 2012). However, the conclusion that the inflammasome in intrinsic renal cells was important in this case is, strictly speaking, not necessarily accurate, as the siRNA was also delivered to intrarenal immune cells such as the network of intrarenal mononuclear phagocytes (macrophages and dendritic cells). Bone marrow chimeric mice, as used in studies of the NLRP3 inflammasome in diabetic nephropathy (Shahzad et al. 2015) may be useful in this context. NLRP3 inflammasome activation may have tissue-specific effects in certain conditions. For example, Bakker et al. used bone marrow chimeric mice to study tubular repair after ischaemia-reperfusion injury (IRI) and found that intrinsic kidney-derived NLRP3 impaired tubular regeneration, whereas leukocyte-associated NLRP3 was associated with tubular apoptosis (Bakker et al. 2014). To add further complexity, it is likely that different types of myeloid cells require different triggers for NLRP3 inflammasome activation. For example, monocytes may respond to purified LPS alone (Netea et al. 2010), and murine neutrophil inflammasomes are not activated by particulate matter as those of macrophages are (Chen et al. 2016). It remains to be seen whether there are specific triggers that cause inflammasome activation in intrinsic kidney cells that differ from the triggers required by immune cells.

8.2.1 Other Inflammasomes in the Kidney

Although a role for AIM2 and NLRC4 inflammasomes in the pathogenesis of several renal diseases has been postulated (Du et al. 2013; Yuan et al. 2016; Zhen et al. 2014), as yet there is little information on the presence of these inflammasomes in intrinsic kidney cells.

8.3 How Does Inflammasome Activation Promote Kidney Injury?

8.3.1 Effects of IL-1β on Leukocytes and Kidney Tissue Cells

The IL-1 receptor (IL-1R) is present on a variety of cell types, including leukocytes and intrinsic kidney cells. It can be bound by either of the isoforms of IL-1, IL-1α or IL-1β, both pro-inflammatory cytokines with similar but slightly distinct biological actions. Pro-fibrotic and inflammatory mediators induced by IL-1/IL-1R interactions include IL-6, tumour necrosis factor (TNF), prostaglandins, TGF-β and tissue matrix metalloproteinases (MMPs), highly relevant to a range of kidney diseases (Gabay et al. 2010). Experiments using mice deficient for the IL-1R highlight the important role of IL-1 in inflammatory cell recruitment to the kidney (although not distinguishing between the actions of IL-1α and IL-1β); IL-1R-deficient mice are protected from acute severe glomerulonephritis, IRI and experimental renal fibrosis (Furuichi et al. 2006; Jones et al. 2009; Timoshanko et al. 2004a). IL-1 (which here refers to both IL-1α and IL-1β) promotes inflammatory cell recruitment both by inducing the expression of adhesion molecules on endothelial cells and promoting the production of chemokines by stromal cells (Gabay et al. 2010). IL-1 also plays a role in adaptive immunity, being important in the differentiation of Th17 cells (Chung et al. 2009).

IL-1 has directly detrimental effects on intrinsic kidney cells. In experimental rapidly progressive glomerulonephritis, bone marrow chimeric studies showed that leukocyte-derived IL-1β mediated its injurious effects via IL-1R present on intrinsic kidney cells (Timoshanko et al. 2004b). IL-1β may play a role in the biological effects of neutrophil gelatinase-associated lipocalin (NGAL). NGAL, though best known as a biomarker of kidney injury, has a number of potential biological roles depending on its iron chelation status. IL-1β is a potent stimulus for NGAL release from proximal tubular and collecting duct cells (Bonnemaison et al. 2017; Konno et al. 2016). Tissue matrix metalloproteinases (MMPs) disrupt the extracellular matrix such as the GBM (but could also limit excessive matrix deposition in fibrosis). Several MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) are secreted by renal cells in response to cytokines, and IL-1β may contribute to MMP induced tissue injury by augmenting inhibition of endogenous MMP inhibitor TIMP-1 in the presence of TNF in mesangial cells (Nee et al. 2007). One study examining the effect of inflammation on lipid metabolism found that

IL-1β treatment caused cultured human mesangial cells to accumulate cholesterol esters, which lead to production of reactive oxygen species (ROS) and endoplasmic reticulum stress (Zhong et al. 2015).

Two mechanisms for inflammasome-mediated podocyte injury have been postulated. The formation of the large intracellular inflammasome complex in podocytes may lead to podocyte dysfunction by interfering with intracellular signalling (Xiong et al. 2015; Zhang et al. 2012). IL-1β (either produced by leukocytes or acting in an autocrine manner) can adversely affect the production of important podocyte proteins such as nephrin (Takano et al. 2007), compromising podocyte structural integrity and function. Human glomerular endothelial cells use all three forms of intercellular junctions, tight junctions, adherens junctions and gap junctions, to assist in the maintenance of glomerular filtration barrier. IL-1β is known to disrupt tight and adherens junctions: in a study where human glomerular endothelial cells were treated with IL-1β, cells showed increased permeability and an increase in expression of VE-cadherin, which may represent a compensatory mechanism against the disruption of the other inter-endothelial junctions by IL-1β (Du et al. 2015).

8.3.2 Effects of IL-18 on Leukocytes and Kidney Tissue Cells

IL-18 was first characterised as a promoter of IFNγ release and in the presence of IL-12 or IL-15 enhances development of Th1 cells. However, in the absence of IL-12 or IL-15, IL-18 has pro-inflammatory actions similar to IL-1 family cytokines (Novick et al. 2013). IL-18 binds to a specific receptor, IL-18R, resulting in a signalling cascade leading to the activation of NF-κB and p38 mitogen-activated protein kinases and the production of downstream pro-inflammatory cytokines (Bombardieri et al. 2007; Yamamura et al. 2001). IL-18 seems to be particularly important in neutrophil activation and recruitment to the kidney, where these cells can then go on to release injurious chemokines, cytokines and ROS (Futosi et al. 2013). IL-18 can also promote the production of pro-inflammatory cytokines by mesangial cells (Schrijvers et al. 2004). In a murine IRI, bone marrow-derived IL-18 was seen to mediate renal injury and was associated with tubular cell damage and increased intrarenal neutrophil and macrophage accumulation (Wu et al. 2008). IL-18 has a local pro-inflammatory and pro-fibrotic role in experimental Th1-dependent GN (Kitching et al. 2005) and unilateral ureteral obstruction (UUO), a model of CKD (Bani-Hani et al. 2009).

Although there is little data on the specific effects of IL-18 on glomerular cells, several studies have focussed on the effect of IL-18 on renal tubular epithelial cells. Both the STAT-3 (Matsui et al. 2013) and TLR4 (Meldrum et al. 2012) pathways in tubular epithelial cells are likely to be important in mediating IL-18's pro-fibrotic effects in unilateral ureteric obstruction mouse models and in vitro in human tubular epithelial cells. IL-18 also induces pro-apoptotic signalling via a FasL-dependent mechanism and may be a significant mediator of tubular cell apoptosis (Zhang et al. 2011).

8.4 Inflammasomes in Acute Kidney Injury

Acute kidney injury (AKI) is an abrupt decline in renal function resulting in the retention of nitrogenous waste, commonly associated by oligoanuria and assessed clinically by serum creatinine and urea measurements. While AKI is often reversible once the underlying insult is treated, it is a global public health concern associated with high morbidity, mortality and healthcare costs (Mehta et al. 2015). AKI has multiple aetiologies, with ischaemic injury to the kidney due to major surgery, sepsis or exposure to nephrotoxins accounting for many cases. While the aetiologies vary between patients, acute tubular necrosis (ATN) is a common histological feature of several forms of AKI, characterised by widespread tubular cell necrosis and the formation of intratubular casts derived from sloughed cells and cellular debris. Damaged tubular and endothelial cells release endogenous DAMPs that activate pattern recognition receptors (PPRs) and initiate innate immune responses. In animal models of AKI, specific components of necrotic cellular debris such as histones, heat-shock proteins, biglycan, HMGB1 and hyaluronan are capable of inducing IL-1β in an NLRP3-dependent manner (Iyer et al. 2009). There is substantial data supporting the role of the inflammasome in numerous models of AKI including IRI, cisplatin-induced nephrotoxicity as well as AKI induced by sepsis, contrast medium and rhabdomyolysis, as summarised in Table 8.3.

8.4.1 Ischaemia-Reperfusion Injury

Renal ischaemia with subsequent reperfusion is a common cause of AKI. In addition, it is an obligatory component of renal transplantation that when severe, leads to delayed allograft function. In murine bilateral renal IRI, NLRP3-deficient mice are functionally protected 24 hours post ischaemia (Iyer et al. 2009), with less intrarenal IL-1β. This protection is associated with fewer infiltrating neutrophils and less CXCL1 (a key neutrophil chemoattractant) in the renal interstitium. However, ASC deficiency shows no protection against early renal dysfunction, although it did provide partial protection after 5 days, with reduced neutrophil recruitment and reduced levels of intrarenal CXCL1 and IL-1β. The pathogenicity of NLRP3 in IRI was confirmed in subsequent studies, but different mechanisms of protection were reported (Kim et al. 2013; Shigeoka et al. 2010). Shigeoka et al. suggested that NLRP3 promoted injury in an inflammasome-independent manner: mice deficient in ASC, caspase-1, IL-1R and IL-18 showed no difference in histological and functional injury 24 hours after ischemia (Shigeoka et al. 2010). However, they observed significantly less renal tubular apoptosis in absence of NLRP3, suggesting that NLRP3 mediated renal IRI by promoting tubular apoptosis. Kim et al. again confirmed a protective effect from IRI in *Nlrp3*$^{-/-}$ mice but, paradoxically, with increased caspase-1 activity (Kim et al. 2013), having previously demonstrated that caspase-1-deficient mice are resistant to IRI. While collectively these studies implicate the NLRP3 inflammasome in pathological acute inflammatory response during

Table 8.3 The function of inflammasome components in experimental acute kidney injury

Acute kidney injury model	Intervention	Renal effect	Canonical or noncanonical signalling	References
Renal ischaemia-reperfusion injury				
	Nlrp3$^{-/-}$	Protective	Both	Iyer et al. (2009), Kim et al. (2013), Shigeoka et al. (2010)
	Asc$^{-/-}$	Equivocal	Canonical	Iyer et al. (2009), Shigeoka et al. (2010)
	Casp1$^{-/-}$	Equivocal	ND	Melnikov et al. (2001), Shigeoka et al. (2010)
	Il1r$^{-/-}$	Equivocal	ND	Haq et al. (1998), Shigeoka et al. (2010)
	IL-1RA	Protective	ND	Rusai et al. (2008)
	Il18$^{-/-}$	Equivocal	ND	Shigeoka et al. (2010), Wu et al. (2008)
	IL-18BP-Tg	Protective	ND	He et al. (2008), Wu et al. (2008)
	Anti-IL-18 Ab	Protective	ND	Melnikov et al. (2001)
Cisplatin nephrotoxicity				
	Nlrp3$^{-/-}$	No difference	–	Kim et al. (2013)
	Asc$^{-/-}$	Protective	Canonical	Chan et al. (2014)
	Casp1$^{-/-}$	Protective	ND	Faubel et al. (2004)
	Il18$^{-/-}$	Protective	ND	Okui et al. (2012)
	Il18ra$^{-/-}$	Worse	ND	Nozaki et al. (2012)
	IL-18BP-Tg	No difference	–	Faubel et al. (2007)
	Anti-IL-18 Ab	No difference	–	Faubel et al. (2007)
	IL-1RA	No difference	–	Faubel et al. (2007)
Sepsis-induced AKI				
	Nlrp3$^{-/-}$	Protective	Canonical	Cao et al. (2015)
	Caspase-1 inhibitor	Protective	Canonical	Cao et al. (2015)
Rhabdomyolysis-induced AKI				
	Nlrp3$^{-/-}$	Protective	Noncanonical	Komada et al. (2015)
	Asc$^{-/-}$	Protective	Noncanonical	Komada et al. (2015)
	Casp1$^{-/-}$	Protective	Noncanonical	Komada et al. (2015)
	Il1b$^{-/-}$	Protective	Noncanonical	Komada et al. (2015)
	Caspase-1 inhibitor	Protective	Canonical	Homsi et al. (2006)
Contrast medium-induced AKI				
	Nlrp3$^{-/-}$	Protective	ND	Shen et al. (2016)

Ab antibody, *IL-1RA* IL-1 receptor antagonist, *IL-18BP-Tg* IL-18 binding protein transgenic mice, *ND* not determined

renal ischemia, the contribution of other inflammasome members in renal IRI remains to be established. As AIM2 binds to cytosolic DNA (Fernandes-Alnemri et al. 2009; Hornung et al. 2009), and necrotic renal tubular cells have been reported to release extracellular DNA following renal ischemia (Jansen et al. 2017), the AIM2 inflammasome may be pathogenic in AKI due to IRI.

Both IL-1 and IL-18 have been implicated in the pathogenesis of AKI due to IRI. The lack of a functional IL-1R limits renal dysfunction in IRI (Haq et al. 1998), and treatment with anakinra, an IL-1R antagonist (IL-1RA), impairs the inflammatory response and accelerates renal repair processes (Rusai et al. 2008). In addition to urinary IL-18 being a biomarker for tubular inflammation and predicting mortality risk after severe AKI (Coca et al. 2008), IL-18 promotes renal macrophage recruitment, with deficiency or neutralisation (via antisera or IL-18 binding protein transgenic mice) protecting mice from IRI (He et al. 2008; Melnikov et al. 2001; Wu et al. 2008).

8.4.2 Cisplatin Nephrotoxicity

Cisplatin is an inorganic platinum-based chemotherapeutic agent widely used in the treatment of many solid-organ malignancies. However, cisplatin nephrotoxicity is a common dose-dependent complication with 25–35% of patients being affected after a single dose of cisplatin treatment (dos Santos et al. 2012). Cisplatin concentrates in the S3 segment of the proximal tubule, where it induces both necrotic and apoptotic cell death, as well as pro-inflammatory responses (Peres and da Cunha 2013). There are conflicting data on the role of inflammasome components and products in cisplatin-induced AKI in mice, caspase-1 activity increases prior to the development of severe renal failure and *Casp1*$^{-/-}$ mice are protected (Faubel et al. 2004), with caspase-1 deficiency attenuating the increased intrarenal IL-1β and IL-18 found in this model (Faubel et al. 2007). However, although *Il18*$^{-/-}$ mice are protected from cisplatin nephrotoxicity with reduced renal dysfunction and accelerated clearance of cisplatin (Okui et al. 2012), IL-18Rα-deficient mice have increased cisplatin nephrotoxicity (Nozaki et al. 2012). Furthermore, inhibition of IL-1β with IL-1RA and IL-18 with the use of IL-18 antiserum and IL-18BP-Tg mice or combination therapy with IL-1RA and IL-18 antiserum seems not to be sufficient to prevent cisplatin-induced renal damage in mice (Faubel et al. 2007).

ASC is increased in the kidneys of mice with cisplatin-induced AKI (Kim et al. 2013), and ASC deficiency is protective against cisplatin nephrotoxicity with reduced renal dysfunction, ATN, and renal IL-1β and IL-17A levels (Chan et al. 2014). NLRP3 is abundantly present in macrophages and renal proximal tubules of normal mice, there are conflicting reports as to whether its expression is increased after exposure to cisplatin in vitro or in vivo and *Nlrp3*$^{-/-}$ mice are not protected against cisplatin-induced AKI (Kim et al. 2013; Lee et al. 2015; Zhang et al. 2014). Zhang et al. explored the role of the purinergic $2X_7$ receptor ($P2X_7R$) in cisplatin-induced AKI (Zhang et al. 2014). $P2X_7R$, a ligand-gated ion channel activated by high concentrations of extracellular ATP, triggers a strong potassium efflux and subsequent NLRP3 activation (Franceschini et al. 2015). Although $P2X_7R$ is not expressed in renal tissues of control mice, it is upregulated in renal tubules after cisplatin administration (Zhang et al. 2014). A selective $P2X_7R$ antagonist

attenuated cisplatin-induced AKI (Zhang et al. 2014). While $P2X_7R$ may have other pro-inflammatory roles, blocking $P2X_7R$ also decreased the expression of the NLRP3 inflammasome components and downstream inflammatory cytokines in the kidney, implicating the $P2X_7R$-NLRP3 axis in cisplatin nephrotoxicity (Zhang et al. 2014).

In addition to mediating NLRP3 inflammasome function, ASC is an adapter protein for several other inflammasome components including NLRP1, NLRC4 and AIM2. NLRP1 is reportedly increased in the kidney after cisplatin administration (Kim et al. 2013). In addition to sensing microbial stimuli, NLRP1 has been reported to detect reductions in cellular ATP. Given that cisplatin alters intracellular ATP levels in proximal tubules, it is plausible that NLRP1 participates in cisplatin-induced AKI (Liao and Mogridge 2013; Miller et al. 2010; Peres and da Cunha 2013). Similarly, AIM2 may also play an important role in cisplatin-induced AKI, as cisplatin binds to DNA causing DNA strand breaks in mitochondrial DNA (Miller et al. 2010).

8.4.3 Sepsis-Induced AKI

Sepsis, a systemic inflammatory response to infection, is the most common cause of AKI (Rossaint and Zarbock 2016). A growing body of evidence suggests that inflammation, oxidative stress, microvascular dysfunction and tubular epithelial responses are involved in the pathogenesis of this complex condition (Zarbock et al. 2014). Several studies have reported on the participation of NLRP3 and its inflammasome components in sepsis-induced AKI using a cecal ligation and puncture (CLP) model (Cao et al. 2015; Wang et al. 2015b; Zhao et al. 2016). Sepsis-induced kidney damage is accompanied by an upregulation of intrarenal NLRP3, ASC and caspase-1 expression and IL-1β and IL-18 in the serum and kidney (Cao et al. 2015). Inhibiting the inflammasome using *Nlrp3*$^{-/-}$ mice and a caspase-1 inhibitor attenuated CLP-induced renal dysfunction and limited renal neutrophil infiltration, ASC and caspase-1 expression and IL-1β and IL-18 level in the serum and kidney (Cao et al. 2015). Other strategies, including low-dose carbon monoxide (Wang et al. 2015b) and sirtuin 3 (a NAD^+-dependent deacetylase that regulates mitochondrial function by limiting oxidative stress) (Zhao et al. 2016), also limit sepsis-induced AKI and downregulates inflammasome components. Collectively these studies provide insight into the role of the NLRP3 inflammasome in sepsis-induced AKI, but further research is required to determine the underlying mechanisms that link NLRP3 activation and sepsis-induced kidney damage.

8.4.4 Rhabdomyolysis-Induced AKI

Rhabdomyolysis is caused by muscle damage due to a range of insults, leading to the release of myoglobin and other intracellular contents. AKI is a common complication of rhabdomyolysis with up to 50% of patients developing some degree of kidney injury

(Gois et al. 2016). The released myoglobin is deposited in renal proximal tubular cells causing inflammation, necrosis and oxidative damage. Inflammasomes have been implicated in glycerol-induced rodent models of rhabdomyolysis-induced AKI (RI-AKI) (Komada et al. 2015). Caspase inhibition limits rat RI-AKI (Homsi et al. 2006), and mice deficient in NLRP3, ASC, caspase-1 or IL-1β were protected from RI-AKI by preventing the initial inflammatory response that mediates renal tubular damage. Increased renal tubular cell NLRP3 expression initiated inflammatory responses and apoptotic cell death, independent of IL-1β processing suggesting a noncanonical role of NLRP3 during this early phase of RI-AKI (Komada et al. 2015). The endogenous danger signal responsible for NLRP3 activation was not identified in the study, although the heme protein hemin, ferrous and ferric myoglobin, released into circulation following muscle damage, did not induce NLRP3 inflammasome activation in primary tubular and collecting duct epithelial cells in vitro (Komada et al. 2015). Uric acid might be the endogenous danger signal activating the inflammasome cascade in RI-AKI (Gois et al. 2016). Allopurinol, used clinically to lower serum uric acid levels, attenuated renal dysfunction in rat RI-AKI and reduced oxidative stress, tubular apoptosis and renal inflammation by inhibiting the inflammasome cascade with reduced active caspase-1 levels (Gois et al. 2016).

8.4.5 Contrast Medium-Induced AKI

With the wide use of iodinated contrast media in radiological procedures for medical diagnosis and treatment of disease, contrast medium-induced AKI (CI-AKI) has become the third leading cause of hospital-acquired AKI (Shen et al. 2016). While the pathogenesis of CI-AKI is not entirely clear, contrast medium seems to have direct cytotoxic effects on renal tubular cells by inducing apoptosis, the generation of ROS, and indirectly by hemodynamic effects (Sadat et al. 2015). Shen et al. showed that the NLRP3 inflammasome mediates CI-AKI through modulating tubular apoptosis both in vitro using a human renal proximal tubular cell line (HK-2 cells) and experimentally in vivo by administering contrast to mice with a single kidney unilateral nephrectomy model with the administration of media (Shen et al. 2016).

8.5 The Inflammasome in Crystal Nephropathies

Crystal nephropathies are a number of acute and chronic kidney disorders related to crystal deposition or formation inside the kidney, most frequently involving the tubulointerstitium. The kidney is highly susceptible to intrarenal crystal formation or deposition because of the high concentration of ions and molecules reached in the tubulointerstitium as a result of glomerular filtration. It is well established that the NLRP3 inflammasome can be activated by crystalline material via potassium efflux secondary to lysosomal rupture in phagocytic innate immune cells (Hornung et al.

2008). Several crystalline substances implicated in kidney disease, including calcium oxalate, monosodium urate, calcium phosphate and cholesterol embolism, are well-characterised activators of the NLRP3 inflammasome (Hutton et al. 2016).

Calcium oxalate is responsible for kidney stones in approximately 70–80% of kidney stone patients (Darisipudi and Knauf 2016). Two key studies have shown that calcium oxalate crystals activate the NLRP3 inflammasome both in AKI (Mulay et al. 2013) and in progressive renal failure (Knauf et al. 2013). Mulay et al. using a mouse model of crystal nephropathy induced by a high oxalate diet comprehensively showed that intrarenal inflammation, tubular damage and renal dysfunction were attenuated in mice lacking ASC and NLRP3 and their downstream mediators MyD88, caspase-1, IL-1R and IL-18 (Mulay et al. 2013). Calcium oxalate crystals activated renal dendritic cells to secrete IL-1β in an inflammasome-dependent manner; ATP released due to calcium oxalate-mediated tubular damage was potentially activating the inflammasome in this setting (Mulay et al. 2013). *Nlrp3*$^{-/-}$ mice are also protected in chronic calcium oxalate-induced renal disease, seen in primary hyperoxaluria and other crystallopathies (Knauf et al. 2013). A recent microarray study also revealed a potential role for ROS in activating the NLRP3 inflammasome via thioredoxin-interacting protein (TXNIP), a crucial protein that plays a role in regulating ROS production in cells, leading to a robust inflammatory response in the kidneys of rats with hyperoxaluria and calcium oxalate nephrolithiasis (Joshi et al. 2015).

Adenine overload also induces intrarenal crystal precipitation resulting in tubular atrophy and renal fibrosis, with a role for inflammasomes. ASC and caspase-1 are pathogenic in adenine-induced renal inflammation and fibrosis in mice (Correa-Costa et al. 2011), and the NLRP3-specific inhibitor CP-456773 blocked NLRP3 activation in dendritic cells and downstream IL-1β and IL-18 production, attenuating renal inflammation and fibrosis in murine crystal nephropathy induced by diets rich in adenine or oxalate (Ludwig-Portugall et al. 2016). However, delayed treatment, although reducing intrarenal inflammasome activation and inflammation, did not reverse renal fibrosis once it was established.

Hyperuricaemia is epidemiologically associated with an increased risk of AKI and progressive CKD (Iseki et al. 2004; Kaushik and Choo 2016; Obermayr et al. 2008). Experimental studies implicate a variety of mechanisms by which hyperuricaemia causes renal disease, including inflammation provoked by monosodium urate crystals (Isaka et al. 2016). Within the kidney, uric acid preferentially precipitates and forms monosodium urate crystals in collecting ducts and even tophi in the surrounding interstitium of the renal medulla (Mulay et al. 2014). In gout, the potential for monosodium urate crystals to induce the NLRP3 inflammasome is well established (Martinon et al. 2006). Similar mechanisms are likely to operate in the kidney, where monosodium urate induces lysosomal rupture when phagocytosed with mitochondrial damage and ROS production (Emmerson et al. 1990). In vitro studies demonstrate that soluble uric acid or monosodium urate crystals induce NLRP3 activation via a TLR4-dependent pathway in both human primary renal proximal tubular epithelial cells and rat mesangial cells (Hong et al. 2015; Xiao et al. 2015a, b). However, at this stage functional data linking monosodium urate crystals with NLRP3 inflammasome activation in animal models of renal disease is lacking.

Uromodulin is a sticky particle-forming protein secreted exclusively by the thick ascending limb of the distal tubule (Anders and Schaefer 2014; Leemans et al. 2014). Due to its adhesive nature, uromodulin coats all particles in the distal tubule including renal crystals. Distal tubular injury facilitates uromodulin leakage into the interstitial compartment, where it acts as a DAMP and activates interstitial dendritic cells in a TLR4- and NLRP3-dependent manner (Darisipudi et al. 2012; Saemann et al. 2005). The particulate nature of uromodulin favours phagocytosis and endosomal destabilisation in dendritic cells, activating the NLRP3 inflammasome (Darisipudi et al. 2012).

Cystinosis, a rare autosomal recessive disease caused by mutations in the *CTNS* gene, is characterised by the lysosomal accumulation of cystine, leading to the formation of cystine crystals in multiple organs, including the kidney. Infantile cystinosis represents the most severe phenotype with progressive renal impairment and end-stage renal disease (ESRD) that may occur before 10 years of age (Darisipudi and Knauf 2016). Cystine crystals are endogenous inflammasome-activating stimuli, implying that the inflammasome plays a role in the pathogenesis of this disease (Prencipe et al. 2014).

8.6 The Inflammasome in Chronic Kidney Injury and Disease

Unilateral ureteric ligation (UUO) in rodents is often used to study mechanisms of renal fibrosis and progressive chronic kidney disease (CKD). Several studies have employed this model to investigate the role of the inflammasome in the development of CKD. Biglycan, an extracellular matrix component and an endogenous ligand for TLR4 and TLR2, acts as a DAMP for NLRP3 inflammasome activation in UUO, initiating caspase-1-mediated maturation and secretion of IL-1β (Babelova et al. 2009). Vilaysane et al. demonstrated that *Nlrp3*$^{-/-}$ mice developed less tubular injury, inflammation and fibrosis after UUO (Vilaysane et al. 2010), a phenotype associated with reduced caspase-1 activation and IL-1β and IL-18 maturation. Bone marrow chimeras revealed these effects were mediated by NLRP3 in both haematopoietic and non-haematopoietic cells, but IL-1β/IL-18 processing in renal tubular epithelial cells could not be detected, suggesting a noncanonical role for NLRP3 in tubular cells (Vilaysane et al. 2010). The same group revealed that NLRP3 promotes pro-fibrotic TGF-β-mediated signalling and Smad2 and Smad3 phosphorylation in renal epithelium independently of forming a caspase-1-activating inflammasome (Wang et al. 2013). However, the role of the NLRP3 inflammasome during UUO remains controversial. ASC-deficient mice have significantly reduced renal inflammatory responses and improved renal injury and fibrosis after UUO (Komada et al. 2014). Mechanistically, this study found that ATP induces inflammasome activation in ASC, expressing collecting duct epithelial cells via P2X-potassium efflux and ROS-dependent pathways in vitro, but this was not

examined in vivo (Komada et al. 2014). Further studies have suggested roles of NLRP3 via promoting mitochondrial dysfunction and the subsequent release of mature IL-1β and IL-18 (Guo et al. 2017), while in UUO, IL-36 signalling may also activate the NLRP3 inflammasome in both immune cells and renal epithelial cells (Chi et al. 2017). Despite the discrepancies in mechanism, most studies have found that NLRP3 signalling promotes injury in UUO. In contrast, at least one study does not support a pathogenic role for NLRP3 with NLRP3 deficiency resulting in increased interstitial oedema and vascular leakage, potentially due to reduced expression of intercellular junction components (Pulskens et al. 2014). Experimental administration of a number of anti-inflammatory mediators such as milk fat globule-epidermal growth factor 8 (Brissette et al. 2016), Danggui Buxue Tang (Wang et al. 2016), aliskiren (Wang et al. 2015c) and fluorofenidone (Zheng et al. 2017) all attenuate experimental renal fibrosis and inflammatory responses after UUO, potentially by inhibiting NLRP3 inflammasome activation. In a cohort of renal biopsies from patients with nondiabetic kidney disease, renal mRNA levels of NLRP3 correlated with renal functional impairment, further supporting that NLRP3 contributes to the pathogenesis of CKD (Vilaysane et al. 2010).

8.6.1 Diabetic Nephropathy

Diabetic nephropathy (DN) is the leading cause of ESKD worldwide and is increasing in prevalence (Molitch et al. 2015). Albuminuria is an early sign of DN, with in many, an irreversible decline in renal function subsequently occurring over years. Unlike Type 1 diabetes mellitus (T1DM), which is an autoimmune disease with destruction of pancreatic islet cells causing insulinopenia, Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance, often seen in concert with other aspects of the metabolic syndrome including obesity, hypertension, hyperlipidaemia and hyperuricaemia. Obesity and hypertension in themselves cause proteinuria and hasten progression of diabetic kidney disease and also contribute to an inflammatory state in which there is aberrant NLRP3 inflammasome activation (Mastrocola et al. 2018). While some processes common to diabetic nephropathy implicate the NLRP3 inflammasome in both Type 1 and Type 2 diabetes, the role of the inflammasome in T2DM bears special consideration, because of the range of substances that may function as inflammasome-activating DAMPs in this condition. This section will focus on the inflammasome in diabetic kidney disease, rather than in diabetes itself or in other aspects of the metabolic syndrome, which is discussed in this chapter (metabolic disease).

Histologically, DN is characterised by glomerular hypertrophy, followed by accumulation of extracellular matrix proteins. Tubular hypertrophy also occurs early and may progress to interstitial fibrosis and tubular atrophy over time (Pourghasem et al. 2015). Macrophages are present in the kidneys of diabetic humans and in rodent models of DN (Chow et al. 2004; Nguyen et al. 2006); the extent of inflammatory cell infiltrate correlates with the decline in renal function, and

CCL2 deficiency in mice limited intrarenal macrophage infiltrates and diabetic nephropathy, suggesting a causative link (Awad et al. 2011; Lim and Tesch 2012). Thus, although it has been known for some time that sterile inflammation is associated with progression of DN, the NLRP3 inflammasome as a link between these two entities has only been explored more recently. Supporting the experimental data detailed below is human data showing that urinary IL-18 and serum IL-1β levels are elevated in patients with diabetic nephropathy compared to diabetic patients without albuminuria, and levels correlate closely with the degree of albuminuria (Nakamura et al. 2005; Shahzad et al. 2015). Additionally, polymorphisms in the promoter region of the IL-18 gene may be associated with the development of diabetic nephropathy in diabetic patients (Elneam et al. 2016).

Various studies have implicated the NLRP3 inflammasome in diabetic nephropathy using mouse models. One of the most comprehensive used both db/db mice, which develop diabetes in the setting of insulin resistance and obesity (modelling T2DM), and uninephrectomised mice treated with the pancreatic β-cell toxin streptozotocin (STZ, modelling T1DM) (Shahzad et al. 2015). While 8-week-old db/db mice do not have signs of renal disease, the development of albuminuria and renal histological changes occurs by 12 weeks. Caspase-1 and NLRP3 deficiency were both protective in the db/db and insulinopenic STZ models. IL-1RA (anakinra) administered to 8-week-old db/db mice for 12 weeks limited albuminuria and extracellular matrix accumulation. IL-1RA was also administered to 12-week-old db/db mice with established renal disease for 8 weeks, resulting in a normalisation of albuminuria and renal histology. Interestingly, though IL-1RA resulted in weight loss and improved blood glucose levels only in the db/db mice, it did not affect metabolic parameters in STZ mice, indicating the renoprotective effect was, at least partially, independent of the observed metabolic improvements. The lack of protection seen in irradiated wild-type mice transplanted with *Nlrp3*$^{-/-}$ or *Casp1*$^{-/-}$ bone marrow and the fact that *Nlrp3*$^{-/-}$ mice transplanted with wild-type bone marrow remained protected indicate that intrinsic renal cell-derived, rather than immune cell-derived, NLRP3 inflammasome activation drives disease. Supporting this, NLRP3 inflammasome activation (in the form of co-localisation of cleaved caspase-1 and NLRP3) was seen both in glomerular endothelial cells and in podocytes of db/db mice and of diabetic humans. Cleaved IL-1β was upregulated in glucose-stressed human podocytes and mouse glomerular endothelial cells compared to cells treated with control substances. This IL-1β production was caspase-1 dependent, indicating canonical NLRP3 inflammasome activation occurred in these intrinsic renal cells.

8.6.2 NLRP3 Inflammasome-Activating Substances in T2DN

There are a number of exogenous and endogenous substances that are present or increased in DN that can also activate the NLRP3 inflammasome; multiple studies have linked a particular inflammasome-activating DAMP to renal disease in T2DM. Several studies point to mitochondrial ROS as being a likely activator of NLRP3-

ASC in diabetic nephropathy, including ex vivo studies in human monocytes and macrophages and db/db mice treated with mitochondrial ROS inhibitor (Mirza et al. 2014; Shahzad et al. 2015). High glucose itself may stimulate the expression of NLRP3 (Chen et al. 2013). A study by Gao et al. found this occurs due to hyperglycaemia-induced expression of thioredoxin-interacting protein, which causes activation of the gp91 (phox) subunit of NADPH oxidase, which then activates NLRP3 (Gao et al. 2015). Islet amyloid polypeptide, produced in response to elevated blood glucose by pancreatic islet cells and secreted with insulin, can activate the NLRP3 inflammasome via disruption of phagolysosomes as well as cathepsin-B and cathepsin-L (Masters et al. 2010). Hyperuricaemia commonly occurs in metabolic syndrome, often found in T2DM. Monosodium urate crystals may act as an inflammasome activator in this situation (Kim et al. 2015). ROS, which are produced in greater amounts in the adipose tissue of obese compared to nonobese individuals (Furukawa et al. 2004), and certain fatty acids (L'Homme et al. 2013; Wen et al. 2011) can also act as an NLRP3 inflammasome-activating signal. In practice, it may be a combination of more than one of these substances that causes NLRP3 inflammasome activation and inflammation in DN.

8.6.3 NLRC4 in Diabetic Nephropathy

Although most studies have focussed on the role of the NLRP3 inflammasome in this disease, NLRC4 inflammasome expression was found to be increased in the kidneys of diabetic humans, and mice deficient in NLRC4 were protected in a STZ model of diabetes, with decreased intrarenal macrophage accumulation (Yuan et al. 2016).

8.6.4 Inflammasome Blocking Treatments for T2DM

Although IL-1 blockade has shown promise in mouse models of DN (Shahzad et al. 2015), trials in humans have focussed on glycaemic control and other metabolic effects rather than renal disease (Larsen et al. 2007; Mandrup-Poulsen et al. 2010). A number of other treatments have been used in mouse models. For example, in an STZ-induced murine model of diabetic nephropathy, with hyperlipidaemia and hyperuricaemia, mice were found to express high levels of NLRP3 and downstream cytokines IL-1β and IL-18. Treatment with allopurinol and quercetin (which have uric acid and lipid-lowering effects) limited NLRP3-ASC inflammasome activation and improved renal histology. Extracellular ATP, an endogenous DAMP activating the inflammasome via the $P2X_7R$, promotes renal interstitial inflammation. Both apyrase, which consumes extracellular ATP, and compounds targeting the $P2X_7R$ limit glucose stimulated NLRP3 expression and IL-1β and IL-18 release (Chen et al. 2013). Although approaches targeting a specific inflammasome activator are useful

in mouse models, their effects may be limited in real-world human disease, unless a unifying inflammasome activator is found.

8.7 Inflammasomes and Glomerulonephritis

Autoimmunity is the predominant pathogenic process underlying most forms of glomerulonephritis (Holdsworth et al. 2016). Autoantibodies may be directed against components of the glomerulus, as occurs in membranous nephropathy and anti-GBM disease. Circulating autoantibodies that target antigens which are not specific to the kidney, such as double-stranded DNA (dsDNA) in lupus, and neutrophil components in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), can also cause kidney injury (Suarez-Fueyo et al. 2017). In some diseases, such as anti-GBM disease, the pathogenic antigen and autoantibody have been well characterised (Ooi et al. 2017), whereas in others, such as idiopathic minimal change disease, a circulating factor causing immune-mediated damage is likely to be present, but is not yet identified (Bierzynska and Saleem 2017). Although part of the innate immune system, inflammasomes can modulate adaptive immune responses, contributing to loss of tolerance and autoimmunity, via effects on T-cell differentiation. Autoreactive $CD4^+$ T cells not only promote autoantibody production (as T follicular helper cells) but also act as local effectors and are key players in a number of renal autoimmune diseases, including lupus (Okamoto et al. 2012), anti-GBM disease (Ooi et al. 2013; Salama et al. 2001) and AAV (Ooi et al. 2012). On activation, naïve $CD4^+$ T cells differentiate into functionally distinct subsets, with characteristic patterns of cytokine secretion. The inflammasome has effects on $CD4^+$ T-cell fate determination via IL-1β and IL-18. IL-18 is important in Th1 responses (Novick et al. 2013), whereas IL-1β is essential for Th17 cell differentiation from naïve T cells (Joosten et al. 2013). As Th1 and Th17 cells actively participate in experimental models of glomerulonephritis (Summers et al. 2011, 2009), the modulation of adaptive immune responses by the inflammasome may be important in a number of autoimmune kidney conditions.

8.7.1 Models of Anti-GBM Disease and Immune Complex Glomerulonephritis

Anti-GBM disease is a rare condition characterised by the deposition of antibodies targeting the non-collagenous domain of type IV collagen (α3(IV)NC1) within the GBM, with glomerular linear IgG deposition seen in kidney biopsies. Disease is mediated by autoreactive T and B cells (Holdsworth et al. 2016) resulting in rapidly progressive glomerulonephritis and often pulmonary haemorrhage, with ESRD and often death if left untreated. Mouse models of ‘anti-GBM disease’ usually involve

injection of heterologous anti-basement membrane globulin raised in another species (sometimes called nephrotoxic serum nephritis). These models, which are not autoimmune, have two phases: the initial (heterologous) phase is the direct effect of the antibodies binding to the GBM; the second (autologous) phase occurs when antibodies and T cells are produced that target the heterologous globulin bound to glomerular capillary walls. While having some value in defining effector responses in severe glomerular disease, autologous phase 'anti-GBM disease' is not autoimmune and should not be confused with true autoimmune models of this disease (Odobasic et al. 2014; Ooi et al. 2014, 2017; Wu et al. 2002).

Endogenous IL-1 and IL-18 are pathogenic in autologous phase 'anti-GBM' glomerulonephritis (Kitching et al. 2005; Lan et al. 1993). $PX2_7R$ is increased in mesangial cells and glomerular macrophages in murine autologous phase 'anti-GBM' glomerulonephritis and in humans with autoimmune GN (Turner et al. 2007). $PX2_7$-deficient mice and mice treated with a $PX2_7$ inhibitor were protected from glomerular injury in autologous phase 'anti-GBM' GN (Taylor et al. 2009). Lichtnekert et al. studied the role of inflammasomes in heterologous phase 'anti-GBM GN' where passive antibody transfer induces leukocyte-mediated injury. Pro-IL-1β, caspase-1, NLRP3 but not ASC mRNA were induced in kidneys of mice injected with anti-GBM. NLRC1, NLRP4 and AIM2 mRNA were undetectable. As in previous studies (Kitching et al. 2005; Lan et al. 1993; Tang et al. 1994; Timoshanko et al. 2004a), IL-1 and IL-18 were both pathogenic, but ASC, NLRP3 and caspase-1 deficiency did not protect against disease. While this study reported that mesangial cells, glomerular endothelial cells and podocytes did not secrete IL-1β (Lichtnekert et al. 2011), several other studies indicate that glomerular cells can produce IL-1β (Table 8.2).

8.7.2 *Lupus Nephritis*

Renal injury in lupus nephritis is mediated by immune complex deposition as well as other effectors, with the role of innate immune pathways being increasingly recognised (Bagavant and Fu 2009). Type I interferon is a central mediator in the pathogenesis of systemic lupus erythematosus (SLE) (Crow 2014), and IL-18, a strong interferon inducer, is increased in the serum of people with SLE, with IL-18 levels correlating with the presence of lupus nephritis and proteinuria (Calvani et al. 2004). IL-18 deficiency in autoimmune-prone Fas-deficient (MRL-Fas^{lpr}) mice prolonged survival and attenuated renal disease (Kinoshita et al. 2004). Several inflammasomes have been implicated in the pathogenesis of SLE. Mouse and human data suggest a role for NLRP3 and AIM2 inflammasomes, and a study of single-nucleotide polymorphisms in seven inflammasome-related genes found that polymorphisms in the NLRP1 inflammasome (but not in AIM2 or NLRP3) were associated with both lupus and the development of lupus nephritis (Pontillo et al. 2012). Intrarenal caspase-1 and NLRP3 are increased in human lupus nephritis (Kahlenberg et al. 2011). The AIM2 inflammasome, activated by cytosolic DNA,

is implicated in people with SLE with AIM2 expression correlating with clinical disease severity (Zhang et al. 2013). In murine lupus induced by apoptotic DNA immunisation, AIM2 expression was increased in renal macrophages and correlated with dsDNA levels. Silencing of AIM2 expression limited autoantibody production and renal disease (Zhang et al. 2013).

In vivo evidence supporting the role of the NLRP3 inflammasome in lupus is found in pristine-induced murine lupus, in which blockade of caspase-1 was protective, resulting in a reduction in autoantibodies, glomerulonephritis and inhibition of the development of the type I IFN response (Kahlenberg and Kaplan 2014). Conversely, mice with a gain of function mutation in NLRP3 in the pristine-induced experimental model develop more severe lupus. This phenotype appears to be related to NLRP3 expression in myeloid cells, because Cre recombinase-mediated deletion of this mutant from myeloid cells resulted in significant reduction in disease (Lu et al. 2017). However in the C57BL/6$^{lpr/lpr}$ model of systemic autoimmunity, both ASC and NLRP3 played a regulatory role, with deficiency of either resulting in the development of more severe autoimmunity and diseases, potentially via effects on the SMAD2/SMAD3 signalling pathway (Lech et al. 2015).

Both dsDNA and neutrophil extracellular traps (NETs) can activate the NLRP3 inflammasome in lupus. dsDNA complexes isolated from SLE patients can activate the NLRP3 inflammasome in human monocytes, in a TLR9- and NF-κB-dependent manner. Blocking ROS production and potassium efflux significantly reduced IL-1β production from dsDNA-treated monocytes, indicating the importance of these processes to NLRP3 activation (Shin et al. 2013). NETs, networks of chromatin fibres laced with antimicrobial peptides and enzymes that can be extruded from neutrophils and macrophages, are thought not only to play an important role in host defence but also in the pathogenesis of a variety of autoimmune diseases (Kahlenberg et al. 2013; Kessenbrock et al. 2009). Both NETs and IL-37, an antibacterial protein externalised on NETs, activated the NLRP3 inflammasome in human and murine macrophages; this NET-mediated activation was enhanced in macrophages derived from lupus patients (Kahlenberg et al. 2013). Interestingly, NETosis in macrophages was also promoted by IL-18, potentially leading to a cycle of NET-induced inflammasome activation (Kahlenberg et al. 2013).

8.7.3 ANCA-Associated Vasculitis

The ANCA-associated vasculitides (AAV) are small vessel vasculitides characterised by autoantibodies specific for neutrophil granule components, myeloperoxidase (MPO) and proteinase 3 (PR3), and inflammatory cell infiltration causing damage to the walls of small- and medium-sized blood vessels. The kidney is a commonly affected organ. In these diseases, ANCA bind to activated neutrophils, causing degranulation and injurious ROS production (Jarrot and Kaplanski 2016). Both IL-18 and IL-1β have been shown to be important in the pathogenesis of AAV. Neutrophils are usually primed prior to ANCA-mediated activation.

Traditionally TNF has been used to prime neutrophils ex vivo, but IL-18 primes neutrophils comparably to TNF (Hewins et al. 2006). Patients with active vasculitis have increased serum IL-18 levels, and IL-18 is also upregulated in the kidney in AAV (Hewins et al. 2006; Hultgren et al. 2007). In humans with MPO-AAV intrarenal IL-1β, TLR4 and NLRP3 expression correlated with the severity of tubulointerstitial injury (Tashiro et al. 2016). Experimentally, IL-1RA treatment protected mice from the development of anti-MPO GN in a bone marrow transplant model of AAV. As mice transplanted with bone marrow deficient in dipeptidyl peptidase, required for neutrophil serine protease activation, were also protected, it was proposed that activation of neutrophil IL-1β by serine proteases was more important than inflammasome-mediated IL-1β activation in this disease (Schreiber et al. 2012). In further work, phagocyte NADPH oxidase, thought to be involved in the production of tissue-damaging ROS, was in fact found to downregulate caspase-1, decreasing inflammasome-dependent IL-1β production and protecting against GN (Schreiber et al. 2015). Although this may indicate that there are two, independently acting pathways by which ANCA induces IL-1β production by monocytes, a neutrophil serine protease pathway and an inflammasome-dependent pathway (Schreiber et al. 2015), further work would clarify the roles of IL-1β and of specific inflammasomes in AAV.

8.7.4 IgA Nephropathy

IgA nephropathy is the most common form of primary glomerulonephritis worldwide and can be diagnosed on renal biopsy by the presence of glomerular IgA deposits and mesangial cell proliferation. Kidney damage occurs due to glomerular IgA immune complex deposition promoting innate immune effectors, with subsequent T-cell activation and inflammation (Coppo et al. 2010; Rifai 2007). Predicting the course of IgA nephropathy can be difficult, with severity ranging from it being a mild, non-progressive disease to it progressing to end-stage renal failure. Clinical features, including hypertension, proteinuria and a reduced eGFR on presentation (Barbour and Reich 2012), as well as renal biopsy features including tubulointerstitial scarring and glomerulosclerosis (Cook 2007), are associated with risk of progression. However NLRP3 expression (primarily seen in renal tubular epithelium) also correlated with progression of kidney disease (Chun et al. 2016). Experimentally IL-1RA-treated mice were protected in experimental IgA nephropathy in which ddY mice spontaneously develop disease (Chen et al. 1997). NLRP3, caspase-1 and IL-1β levels were significantly increased in a passively induced mouse model of IgAN; and NLRP3-deficient mice were also protected in a passive model of IgA nephropathy, with reduced renal macrophage, dendritic cell and T-cell infiltration, reduced T-cell activation and increased T regulatory cells compared to wild-type mice (Tsai et al. 2017). The recent comprehensive study by Tsai et al. demonstrates the role that the NLRP3 inflammasome plays in linking IgA immune complex deposition and T-cell activation. In in vitro studies, IgA immune complexes

caused NLRP3-dependent IL-1β production in macrophages and dendritic cells, with both canonical (involving caspase-1) and noncanonical pathways (involving caspase-11 in mice, equivalent to caspase-4/5 in humans) being activated. IgA immune complex-primed bone marrow-derived dendritic cells (BMDCs) from wild-type mice induced proliferation of $CD4^+$ T cells and their production of pro-inflammatory cytokines such as IL-17 and IFNγ. T-cell proliferation and cytokine production were greatly reduced when BMDCs from NLRP3-deficient mice were used. The NLRP3 inflammasome activators in this instance were proposed to be IgA immune complex-induced mitochondrial ROS and mitochondrial DNA release into the cytosol. Supporting this, treatment with a mitochondrial ROS inhibitor reduced NLRP3 expression and IL-1β secretion in IgA immune complex-activated macrophages. Additionally, IgA immune complexes were shown to induce NLRP3-dependent IL-1β from primary mesangial cells and renal tubular endothelial cells, indicating NLRP3 inflammasome activation in these intrinsic kidney cells (Tsai et al. 2017).

8.7.5 Inflammasomes in Other Glomerular Diseases

NLRP3 expression has been assessed in kidney biopsies of patients with a variety of nondiabetic kidney diseases with increased NLRP3 and caspase-1 mRNA expression found in all subgroups of kidney disease (Vilaysane et al. 2010; Xiong et al. 2015). In one of these studies, NLRP3 expression correlated with renal impairment and glomerular sclerosis on biopsy, a marker of advanced kidney damage (Xiong et al. 2015), suggesting that NLRP3 might be a common pathway in the progression of disease. Focal and segmental glomerulosclerosis (FSGS) is a kidney disease that can occur in a primary, autoimmune form, or in a secondary form as a result of another insult to the kidney, such as hypertension, obesity or diabetes. Astaxanthin, a compound which exerts suppressive effects on NLRP3 inflammasome activation as well as antioxidant effects, was renoprotective in a mouse model of FSGS induced by Adriamycin (Liu et al. 2015). However, the potential roles of inflammasomes in FSGS and other glomerular diseases such as membranous nephropathy and minimal change disease have not yet been defined.

8.8 Conclusions and Future Directions

While there is much still to learn, there is clear evidence that inflammasomes are relevant to a variety of renal diseases and represent potential therapeutic targets. Ideally a ‘common pathway’ involved in multiple renal diseases may be identified, disruption of which can treat a number of human kidney diseases. However, the wide variety of causes (and therefore mechanisms of disease) imply that detailed studies of multiple types of kidney disease are likely to be required, with clinical

observations being backed by mechanistic and functional studies in relevant in vitro and in vivo models of disease. The advent of more specific inflammasome inhibitors emphasises the need to understand how different inflammasomes contribute to disease in preclinical models.

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