Renal involvement in autoinflammatory diseases and inflammasome-mediated chronic kidney damage

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ABSTRACT

Unprovoked activation of innate immune pathways and increased secretion of interleukin (IL)-1β and IL-18 are responsible for the protean clinical manifestations and the marked inflammatory response that characterise most hereditary autoinflammatory disorders. The kidney is a major target organ of this inflammatory process. The deposition of the acute-phase reactant serum amyloid A (SAA) as amyloid causes progressive glomerular and vascular damage and leads to organ failure. In this review we focus on the potential impact of hereditary autoinflammatory diseases on renal function, provide red flags that may guide the clinical suspicion of amyloid kidney damage and discuss the relevance of close renal monitoring for early diagnosis and prompt treatment. Moreover, NLRP3 inflammasome activation is increasingly recognised to play a key causative role in the pathogenesis of several chronic kidney diseases in which activation of caspase-1 and the proteolytic cleavage of IL-1β and IL-18 into their biologically active forms mediate glomerular and tubulointerstitial damage. Although much of the knowledge about the role of the inflammasome in kidney injury has been mostly gathered in experimental models, inhibition of IL-1 is also becoming an attractive potential therapeutic target in a variety of chronic renal disorders with a substantial inflammatory component.

Introduction

Hereditary autoinflammatory diseases (AIDs) are disorders of the innate immune system characterised by unprovoked attacks of fever and systemic inflammation in the absence of autoantibodies and autoreactive T cells (1). The molecular mechanisms underlying AIDs relate to impaired intracellular danger signalling and/or aberrant inflammasome activation, leading to dysregulation of the inflammatory response and overproduction of proinflammatory cytokines, especially interleukin (IL)-1β (2). Increased IL-1β secretion is responsible for most of the systemic features of this group of disorders and for the persistent acute-phase response associated with them (3). The kidney is a major target organ of this inflammatory process. Kidney damage is mediated by the deposition of the acute-phase reactant serum amyloid A (SAA) as amyloid, which causes progressive glomerular and vascular damage and leads to organ failure. AA amyloidosis is therefore a serious complication of this group of disorders and represents a medical challenge with relevant unmet needs (4).

Major progress in understanding the molecular mechanisms that trigger hereditary AIDs has contributed to highlight the role of immune-mediated inflammation also in more prevalent, acquired conditions including diabetes, obesity, atherosclerosis, crystal-related diseases and neurodegenerative disorders (5, 6). In addition, aberrant renal danger signalling and innate immune activation have also been shown to contribute to the inflammatory process associated with many acute and chronic kidney disorders (7, 8). The inflammasomes, a family of large subcellular multiprotein complexes that sense cellular stress signals and trigger inflammatory responses, are emerging as key mediators of innate immune activation in these multifactorial conditions. In particular, a pivotal role is played by the NLRP3 inflammasome, whose activation is induced by diverse pathogens and host-derived signals of cellular damage [reviewed in (9, 10)] and results in proteolytic cleavage of caspase-1 into its biologically active form, which in turn mediates the production of IL-1β and IL-18 pro-inflammatory cytokines (11).
In this review we focus on the multi-
ple, intertwined mechanisms that link autoinflammation and kidney injury. On the one hand, AIDs may affect re-
nal function through amyloid-mediated
damage, on the other hand, increasing
evidence indicates that NLRP3 inflam-
masome activation and IL-1β-mediated
vascular harm play a role in the patho-
genesis of several chronic kidney dis-
cases. This suggests that targeting these
mechanisms may improve the outcome of several renal disorders with a sub-
stantial inflammatory component.

Autoinflammatory diseases and
amyloid-mediated renal damage
Unprovoked activation of innate im-
munie pathways and increased secre-
tion of IL-1β and IL-18 are responsible for
the protein clinical manifestations
and the marked inflammatory response
that characterise most hereditary auto-
inflammatory disorders (11). A persist-
tently or recurrently elevated concen-
tration of the circulating acute-phase
reactant SAA is therefore a hallmark of
these diseases but also predisposes to
the self-aggregation and extracellular
deposition of this protein as insoluble
amyloid fibrils in different tissues.

AA amyloidosis is one of the best
caracterised systemic forms of amy-
loid disease (12). AA amyloid tissue
pathology and fibril composition have
long been investigated in humans and
animals (13), and seeding, accumula-
tion and clearance of AA deposits have
been shown in several experimental
models (14-17). However, the molecu-
lar mechanisms underlying misfolding
and aggregation of this protein into
cross-β-sheet fibrillar deposits and the
reasons for preferential accumulation in
the renal glomeruli in humans are
far from being clarified (13).

Whereas a persistently elevated con-
centration of SAA is a prerequisite for
AA fibrillogenesis, its physiological
role in acute and chronic tissue injury
is not fully understood. However, evi-
dence points to an evolutionary con-
served function of this protein in pro-
moting the mobilisation and recycling
of cholesterol from damaged tissue for
cell repair (18). Following secretion by
hepatocytes, SAA rapidly binds through
its N-terminal domain to the surface of
high-density lipoproteins (HDL) and,
by displacing apolipoprotein A-I and
other apolipoproteins, redirects them
towards tissue macrophages, where it
activates cholesterol efflux. The intrin-
sically disordered structure of SAA,
that at near-physiological conditions
spans multiple conformations, supports
its ability to interact with multiple li-
gands, including lipids, cell receptors,
and proteoglycans (19). Interactions
with glycosaminoglycans and mac-
rophages have been shown to promote
both the dissociation of SAA from HDL
(18, 20, 21) and its proteolytic remod-
elling by one or more as yet unidenti-
ﬁed enzymes, releasing the N-terminal
cleaved fragments predominantly span-
ning the first 76 amino acids that are
ultimately found in AA amyloid fibrils.

Interestingly, an association between
AA fragment length, intensity of amy-
loid birefringence and pattern of renal
deposition has been reported, suggest-
ing that cleavage is a key and specific
event that drives SAA fibrillogenesis
and tissue pathology (13).

Clinically, AA amyloidosis presents
in its early stages with a low-grade
proteinuria that usually progressively
worsens if the inflammatory stimulus
persists or recurs over time, leading
to nephrotic syndrome and ultimately
renal failure. Advanced renal dysfunc-
tion at diagnosis and persistent el-
vation of SAA during follow-up are
powerful risk factors for progression to
end-stage renal disease (ESRD) and
death (22). Recently, we reported that
renal survival was independently pre-
bicted by proteinuria (>4 g/day) and
estimated glomerular filtration rate
(<35 ml/min) at diagnosis, establishing
a staging system that identiﬁes patients
at higher risk for progression to ESRD
and dialysis (23). A delay in diagno-
sis therefore dramatically impacts on
patients’ quality of life and survival.
However, renal failure due to AA amy-
loidosis is still the presenting feature
that prompts clinical suspicion and di-
agnostic work-up for a hereditary AID
in several cases (24).

Although kidney damage usually dom-
inates the natural history and clinical
presentation, AA amyloidosis is a sys-
temic disease and therefore other signs
and/or symptoms should also herald
the diagnostic suspicion (Fig. 1). Gas-
trointestinal manifestations, includ-
ing bowel abnormalities and gastric
symptoms such as heartburn, nausea,
and vomiting, hepatosplenomegaly
and orthostatic hypotension related to
autonomic dysfunction may variably
associate with kidney damage over the
disease course. Sometimes progressive
thyroid enlargement is observed, with
preserved hormonal secretion (25).

Compared with AL and ATTR amyloi-
dosis, cardiac involvement is quite un-
usual at disease onset although it may
occur with time and negatively impact
on survival in patients that require di-
alysis. Infertility due to progressive
ovarian infiltration has been reported
in young men with untreated familial
Mediterranean fever (FMF) (26).

Symptomatic adrenal insufﬁciency due
to massive gland inﬁltration has been
observed in advanced stages and may
complicate the management of patients
undergoing renal transplantation (27).

Diagnosis requires demonstration
of amyloid deposits in a tissue biopsy
coupled with typing by immunohisto-
chemistry or by proteomics-based tech-
niques (28). Although amyloid infiltra-
tion is expected in AIDs, non-amyloid
nephropathies have been reported in a
proportion of FMF patients in differ-
ent series, as discussed later (29). This
points to the necessity of a histological
proof of amyloid deposition in all pa-
ients with an AID who develop renal
dysfunction. Moreover, accurate deﬁ-
nition of the amyloidogetic precursor
has been thoroughly highlighted as a
potential pitfall in the diagnosis of any
systemic amyloid disease. AA amyloi-
dosis is a long-term complication of
AIDs as well as of many other chronic
inflammatory conditions and mostly
occurs in adult life, thus coexistence
with a monoclonal gammapathy of
uncertain signiﬁcance is possible and
requires the unequivocal characterisa-
tion of amyloid at the molecular level
to rule out the most common AL amy-
loidosis. Non-invasive approaches,
including an abdominal fat aspirate, a
minor salivary gland or a gastroduo-
denal biopsy, should ﬁrst be taken into
consideration in order to minimise bleeding risks, although the feasibility of kidney biopsy is now widely supported in experienced centres (30).

Prevention of AA amyloidosis is mandatory in patients diagnosed with a hereditary AID. Although no evidence-based guidelines are available to address optimal monitoring of AA risk, accurate surveillance can be performed by means of a periodic assessment of inflammatory markers and microalbuminuria during symptom-free intervals. Where available, evaluation of asymptomatic amyloid deposition in liver, spleen and kidneys using serum amyloid P component scintigraphy has been proposed. Beyond the intensity and duration of the systemic inflammatory process, additional factors that modulate the occurrence of AA amyloidosis have been identified (4). In particular, allelic heterogeneity at the \textit{SAA1} locus, resulting in different genotypes, has been shown to play a role in promoting or reducing the risk of amyloid formation (31). Homozygosity for the \textit{SAA1.1} allele is associated with a significantly higher risk of developing AA amyloidosis in Caucasians, whereas susceptibility is increased in individuals carrying only the \textit{SAA1.3} isoform in the Japanese population (32). The underlying mechanisms and the reasons for this discrepancy are far from being clarified, although it has been suggested that they might be related to a variable susceptibility of the different SAA isoforms to proteolytic cleavage (33). In clinical practice, assessment of the \textit{SAA1} genotype may provide invaluable information for the management of patients with a poorly controlled hereditary AID, allowing the guidance of treatment choices and target SAA suppression according to risk.

Whether other mechanisms have an impact on the risk of kidney damage and/or its progression in AIDs is not known. The inflammatory process that takes place in AIDs is not expected to directly injure the kidneys but, at least in FMF, there is evidence that 40-50% of patients presenting with proteinuria are not affected by renal amyloidosis and otherwise suffer from a primary glomerulopathy (29). Interestingly, a significant contribution is represented by IgA nephropathy (IgAN), the most common primary glomerulonephritis (34). Recently, the outcome of kidney donors who carry a \textit{MEFV} gene mutation was compared with that of control donors (35). This study showed that MEFV carriers had a significantly higher 24-hour proteinuria compared with the control group ($p=0.004$) four years after the donation raising the question whether this could be related to a subclinical inflammatory profile of these individuals. In this respect, increasing evidence linking innate immunity and NLRP3 inflammasome activation to the pathogenesis of several forms of acute and chronic kidney disease highlights the question as to whether additional local inflammatory mechanisms might also contribute to renal damage in patients with AIDs.

**The role of the NLRP3 inflammasome in chronic kidney disease**

Inflammation is known to play a role in the development of many acute and chronic non-infectious renal diseases, contributing to the extent of kidney damage and to the severity of organ dysfunction (36, 37). The inflammatory process is mediated by different pro-inflammatory cytokines that induce recruitment and infiltration of mononuclear inflammatory cells in renal tissue (38). The presence of these...
cells in the damaged renal interstitium has been shown to correlate inversely with renal function (39, 40). Infiltration of inflammatory cells is responsible for tissue remodelling and kidney damage, including disruption of tubular integrity, accumulation of fibroblasts, tubular atrophy, and deposition of extracellular matrix molecules. These pathophysiological events are invariably associated with renal function deterioration (41), and consistently, interstitial inflammation and fibrosis are main predictors for the risk of progression towards ESRD (42).

In recent years, increasing research has been devoted to unveiling the molecular mechanisms involved in inflammation-mediated kidney damage. Circulating levels of both the proinflammatory cytokine IL-1β and its naturally occurring receptor antagonist (IL-1Ra) are elevated in chronic kidney damage (CKD) and in dialysis patients, as also are IL-6 and IL-18 (8, 43, 44). Based on these findings, and on evidence that the NLRP3 inflammasome is involved in acute kidney injury in experimental renal ischaemia-reperfusion injury (45), investigations have progressively focused on the role of innate immunity, danger signalling, and inflammasome activation in the pathogenesis of CKD (46).

The role of the NLRP3 inflammasome in mediating renal inflammation in CKD was originally investigated in unilateral ureteral obstruction (UUO), the experimental mice model of chronic progressive renal injury. NLRP3 -/- mice had less tubular injury, inflammation, and fibrosis after UUO, associated with a reduction in caspase-1 activation and maturation of IL-1β and IL-18, compared with wild-type mice (47). In human CKD, up-regulation of the NLRP3 inflammasome was observed in kidney biopsies from a wide variety of non-diabetic kidney diseases, addressing the functional role of the caspase1-IL-1β-IL-18 cascade in mediating inflammatory damage (47). Inflammasome components are expressed in renal dendritic cells and macrophages and mediate NLRP3 canonical function, resulting in increased IL-1β secretion. Expression has also been observed in renal non-immune cells, including tubular epithelial cells. Renal interstitial inflammation has also been reported in kidney biopsies from patients affected by diabetic nephropathy (48) and localises in renal tubular cells.

Overall, there is increasing evidence, mostly gathered through experimental disease models, that the NLRP3 inflammasome plays a major role in mediating the inflammatory response underlying chronic tubulointerstitial diseases, including UUO, glomerulonephritis, and calcium oxalate crystal nephropathy (46).

Although it was initially reported that glomerular parenchymal cells fail to produce IL-1β during sterile inflammation and the NLRP3 axis does not contribute to glomerular inflammation (49), activation of the inflammasome has more recently been suggested to play a role in different glomerular disease murine models. Experimentally, hyperhomocysteinemia (hHcys)-induced glomerular injury was demonstrated via formation and activation of the NALP3 inflammasome complex in podocytes, resulting in podocyte injury and glomerular inflammation, leading to glomerulosclerosis, independently of hypertension (50). Several studies indicate a crucial role of hHcys in the development and progression of renal damage associated with local inflammation, oxidative stress, impaired cell metabolism and consequent fibrogenesis; indeed, NLRP3 was reported to be activated in podocytes during hHcys (50). Treatment of podocytes with l-homocysteine induced the formation of NLRP3 inflammasome complex, an increase in caspase 1 activity, rearrangement of the podocyte cytoskeleton, and decreased production of vascular endothelial growth factor (51). Reactive oxygen species (ROS) production observed in hHcys has been suggested to play a role in NLRP3 activation in podocytes and ultimately, glomerular injury. Furthermore, considering that glomerular VEGF is primarily produced in podocytes and hHcys-treated podocytes display significantly impaired secretion of VEGF, it was recently shown that hHcys treatment significantly increased cleavage of pro-caspase-1 into active caspase-1, an important parameter of inflammasome activation (52). This study also reported that docosahexaenoic acid, a well-known ω-3 polyunsaturated fatty acid, suppressed inflammation via abrogating hHcys-induced podocyte injury by inhibition of the NLRP3 inflammasome activation. However, whether these cells undergo NLRP3 upregulation and have a functional role in canonical inflammasome activation in humans remains elusive and a non-canonical NLRP3 role in mediating fibrosis has been suggested (53).

Recently, several studies suggest that the NLRP3 inflammasome may also be implicated in the pathogenesis of the most common primary glomerulonephritis, IgAN, characterised by various degrees of intrinsic cell proliferation, especially of mesangial cells. Compared with control kidneys, NLRP3 gene expression was reported to be increased in renal biopsies of patients with IgAN and to correlate with disease clinical outcomes (54). This study also showed that although NLRP3 expression in IgAN was detected in glomeruli, it remained mostly confined to the tubular epithelial compartment.

Overall, the causal relationship between the inflammasome and the pathogenesis of IgAN is yet to be determined. A recent study has suggested the NLRP3 inflammasome plays a pathogenic role in the development of IgAN in part by activation of T cells, and mitochondrial damage and ROS production (55). Renal protein levels of NLRP3, IL-1β, and IL-18 were significantly increased in the IgAN model in wild type mice and, moreover, improved proteinuria and renal function and milder renal lesions in IgAN in NLRP3 knockout mice was reported.

Proteinuria activates NLRP3 inflammasome upregulation

Proteinuria has been reported as an independent prognostic factor for long-term renal disease progression, and reduction of urinary protein excretion limits renal function decline in patients with non-diabetic and diabetic nephropathies associated with remodelling of the glomerular architecture.
(56). Increased proinflammatory cytokine secretion mediates progressive proximal tubular damage and interstitial fibrosis associated with exposure to proteinuria. In a mouse model, albumin overload activates NLRP3 inflammasome by ROS (52). Fang et al. have elegantly shown that NLRP3 activation in kidney biopsy specimens was associated with the degree of albuminuria and that in vitro inflammasome upregulation depends on endoplasmic reticulum stress induced by albumin (57). Albumin reabsorption mediated by megalin/cubilin endocytic receptors on tubular epithelial cells leads to lysosomal dysfunction and cathepsin B release, which induces NLRP3 activation. Consequently, inhibition of cathepsin B or megalin/cubilin reduces albuminuria-induced tubular damage (57). Proteinuria may also act on podocytes. Furthermore, podocyte loss via apoptosis may be important in the development of glomerulosclerosis, as described in the model reported by Li et al. (52), in which the link between NALP3 inflammasome and podocyte damage was described experimentally in hHcys-induced glomerular injury.

Management of inflammation-mediated kidney damage: AA amyloidosis and beyond
AA amyloidosis is still a challenging complication of hereditary AIDs, with prognosis depending on both early diagnosis and prompt management of the underlying inflammatory process. Rapid and effective suppression of SAA is associated with a favourable outcome, provided kidney failure is not too advanced (23). Management should aim at normalising SAA and C-reactive protein concentrations (22) within the shortest period of time. Thus, a close assessment of both inflammatory markers is mandatory to carefully monitor treatment response and guide the management strategy. The need for a rapid and effective suppression of the amyloidogenic precursor, combined with the increasing availability of specific drugs that inhibit either IL-1β or IL-6, the two proinflammatory cytokines that regulate SAA hepatic transcription, has progressively changed the management approach to AA amyloidosis. Although colchicine is still recommended in patients with FMF-related AA amyloidosis, the key role of IL-1β in the pathogenic cascade of this disease should prompt us to consider IL-1β inhibition as the first-line option in these patients, particularly when reduced renal function and/or possible gastrointestinal amyloid-related abnormalities may limit colchicine safety, with suboptimal treatment response at the maximum tolerated doses. However, association with colchicine during treatment with a biological agent is still recommended in FMF, whenever possible, based on the long-term evidence of its beneficial effect on AA amyloidosis in this context (58). Several reports have documented the rapid and dramatic response to IL-1 inhibition in patients with renal amyloidosis due to FMF, with a reduction in proteinuria and stability in kidney dysfunction, combined with a good safety profile (59-61).

Extensive experience has been consistently gathered in cryopyrin-associated periodic syndrome (CAPS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) patients affected by renal AA amyloidosis with severe nephrotic range proteinuria and renal insufficiency (62, 63). More recently, the same approach has been used in patients with MVK deficiency developing renal amyloid complications. Unfortunately, response to IL-1 inhibition is less satisfactory in this patient population, whom possibly have more complex molecular mechanisms involved (64, 65). As IL-6 is the major driver of SAA secretion, IL-6 inhibition appears to be a successful tool in all patients with renal AA amyloid disease refractory to previous treatments (66). However, the long-term safety profile of this approach and its feasibility in patients that are known to be at higher risk for infectious complications, remains to be established.

Targeting the inflammasome in chronic kidney diseases
Although much of our knowledge regarding the role of the inflammasome in kidney injury is limited to experimental models and its contribution to human renal disease has yet to be fully elucidated, the inflammasome is an attractive potential therapeutic target not only in renal AA amyloidosis but also in a variety of non-amyloid chronic renal disorders (36, 37). Moreover, IL-1 inhibition may be addressed to target the chronic systemic inflammatory process that is associated with CKD. Circulating levels of both the proinflammatory cytokine IL-1β and its naturally occurring receptor antagonist (IL-1Ra) have been reported to be elevated in patients with CKD, regardless of the aetiology (8, 43, 44). Cardiovascular (CV) risk is substantially increased in patients with CKD who exhibit chronic systemic inflammation. Because chronic inflammation contributes to vascular dysfunction, it has been proposed that blocking inflammation may reduce CV risk in patients with CKD (67).

Conclusions
A long-lasting, systemic inflammatory process, as observed in inadequately treated or late-recognised hereditary AIDs, may lead to the development of AA amyloid-related organ damage, particularly at the kidney level. This complication has a dramatic impact on the natural course of AIDs, significantly worsening a patients’ prognosis and quality of life. Promoting awareness is of the utmost importance in light of the availability of effective management approaches that specifically switch-off the underlying IL-1β-mediated inflammatory process, potentially reverting organ damage and improving the outcome when established in the very early disease stage.

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