

COMMENTARY



## DDR1: A major player in renal diseases

Aude Dorison , PhD and Christos Chantzi Antoniou, PhD

Inserm UMR S 1155 and Sorbonne Université, Paris, France

### ABSTRACT

Discoidin Domain Receptor 1 (DDR1) belongs to a family of two non-integrin collagen receptors, DDR1 and DDR2, which display a tyrosine kinase activity. DDR1 has been widely studied in different kind of pathologies including chronic kidney diseases (CKD). The aims of this commentary are 1. to review the existing information about DDR1 expression in healthy and diseased kidney, 2. to comment the data highlighting DDR1 as a major actor in CKD, 3. to suggest areas of research which require further investigation to better characterize the signaling pathways regulating DDR1 role in CKD.

The results recapitulated in this commentary emphasize the involvement of DDR1 in the pro-inflammatory and pro-fibrotic processes which drives the development of CKD. They also underline the beneficial effect of its blockade in pre-clinical models and thus, reinforce its status of interesting therapeutic target.

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### Introduction

In the early 90's, the two members of the Discoidin Domain Receptors (DDRs) family were discovered: DDR1 and DDR2. They are non-integrin collagen receptors, which display a tyrosine kinase activity [1]. Five isoforms derived from an alternative splicing have been identified for DDR1 (DDR1a to DDR1e), whereas only one isoform exist for DDR2 [2].

Both receptors display a similar structure containing two globular extracellular domains, followed by a unique transmembrane region continuing with a long juxta-membrane domain and a catalytic tyrosine kinase domain ending with a short C-terminal tail [3]. DDR1 isoforms differ in their intracellular region leading to length modification (DDR1a to DDR1c) or kinase inactivation (DDR1 and DDR1e). The most frequently expressed isoforms are DDR1a and DDR1b [2].

Through their globular domains, DDrs can bind several types of collagens comprising collagen type I-IV, VIII and XV for DDR1 and type I-III and X for DDR2 [3–9].

In contrast with the activation of other tyrosine kinase receptors, DDrs phosphorylation occurs slowly upon collagen binding and is maintained overtime [4,5]. DDR1 activation is followed by the shedding of its

extracellular domain through an unknown molecular mechanism [10,11].

The expression and activity of DDrs have been studied in various types of cancer as well as inflammatory and fibrotic diseases. In this commentary, we will focus on the role of DDR1 in chronic kidney diseases (CKD).

### DDR1 Expression in healthy and diseased kidney

#### DDR1 in physiological conditions

While no systematic analysis of DDR1 expression has been published, several studies have focused on the role of DDR1 in kidney. Consistent with the literature, most of them reported the presence of DDR1 in vascular smooth muscle cells (SMC) [12–17] (Table 1). Moreover, a basolateral expression of DDR1 has been described in renal epithelial cells of distal tubules in rat and mouse [12,16]. However, there are conflicting reports regarding DDR1 glomerular expression in healthy kidney. Indeed, DDR1 expression was detected in primary mesangial cell cultures [18] as well as in healthy glomeruli [14,19]. On the other hand, several studies showed immunostainings with a weak or absent expression of DDR1 in mouse [13,15–17], rat [12] and human [15] glomeruli.

**CONTACT** Christos Chantzi Antoniou, PhD  [christos.chatzi Antoniou@upmc.fr](mailto:christos.chatzi Antoniou@upmc.fr)  Inserm UMR S 1155 and Sorbonne Université, Paris, France, Tenon Hospital, 4 rue de la Chine 75020 Paris, France.

Current address: Victor Chang Cardiac Research Institute, Developmental and Stem Cell Biology Division, Level 7, Lowy Packer Building, 405 Liverpool street, Darlinghurst 2010 NSW, Australia. Email address: a.dorison@victorchang.edu.au.

Tenon Hospital, 4 rue de la Chine 75020 Paris, France. Email address: christos.chatzi Antoniou@upmc.fr

**Table 1.** Summary of DDR1 expression profiles in physiological and pathological conditions reported in rodent and human kidney.

Conditions	DDR1 in mouse	DDR1 in rat	DDR1 in human
Healthy or control kidney	SMCs [13-17], distal tubule [16], glomeruli (present [14,19], weak or absent [13,15-17])	SMCs [12], distal tubule [12], glomeruli (absent [12]) Hypertrophic glomeruli [12]	SMCs [15], glomeruli (absent [15])
Remnant kidney model			
Hypertensive nephropathy	Over-expression in SMCs and glomerular tuft [13]		
NTS-induced glomerulonephritis	Podocytes and injured tubular cells [15,16]		
HANAC syndrome	Activated parietal epithelial cells [17]		
UUO model	Tubules, macrophages and glomeruli [14,16]		
Lupus nephritis			Podocytes and crescentic formations [15]
Goodpasture's syndrome			Podocytes and crescentic formations [15]

Despite the expression profile of DDR1, mice lacking this gene didn't display any major renal phenotype [20]. An initial study described a mushroom-like isodense thickening of the glomerular basement membrane (GBM) in DDR1 knockout (KO) mice, which was associated with low levels of proteinuria [19,21]. However, this phenotype affected a low percentage of glomeruli in old mice and uremia, an indicator of renal function, remained within the normal range in DDR1 KO [19,22].

### DDR1 in pathological conditions

In pathological conditions, DDR1 expression is rather dependent on the site of injury. The first report describing DDR1 expression profile after renal injury was published in 2004. Lee R and colleagues [12] used the remnant kidney model where male Sprague-Dawley rats underwent a right nephrectomy followed by a partial renal infarction. This led to an increased expression of DDR1 in hypertrophic glomeruli next to the scar area, but not in the interstitium. In a recent study, Borza CM and colleagues [23] used a similar model, the 5/6 nephrectomy, in which the upper and lower poles of the right kidney were resected before to perform a left nephrectomy. Their results indicated a significant improvement of the disease outcome in DDR1 KO mice compared to wild type (WT). However, there was no information on DDR1 expression profile in this model.

Other studies demonstrated an induction of DDR1 expression in the glomerulus, in various cell types. In 2006, we studied DDR1 in a model of hypertensive nephropathy induced by continuous subcutaneous infusion of angiotensin II for 4 or 6 weeks [13]. This treatment induced an overexpression of DDR1 in vascular SMC and in the glomerular tuft, presumably in the mesangium. In another report, we used the nephrotoxic serum (NTS)-induced glomerulonephritis model mainly targeting podocytes, a terminally differentiated epithelial cell type in the glomerulus [15,16]. In this model, we have demonstrated that DDR1 was induced in these specialized epithelial cells as well as in suffering tubular cells.

Mice with the HANAC Syndrome mutation in the Col4a1 gene exhibit diverse renal defects including glomerular cysts, abnormal structure of Bowman's capsule associated with periglomerular and arteriolar inflammation, and parietal cell activation [17]. DDR1 abnormal expression was detected in activated parietal epithelial cells in mutant mice but not in WT. Mice lacking Col4a3 gene, a model of Alport's Syndrome, in combination with *Ddr1* gene invalidation or not were also analyzed [22]. This work demonstrated a protection of mice lacking DDR1 but its expression profile was not described in that article.

DDR1 profile was also examined in the unilateral ureteral obstruction (UUO) model in which the left ureter is ligated at two separate points while the contralateral kidney remains untouched [14,16]. In this model, DDR1 was expressed in suffering tubules, activated macrophages and glomeruli. Finally, we have identified a de novo expression of DDR1 in glomeruli (specifically podocytes/crescents) of patients suffering from lupus nephritis and Goodpasture's syndrome, two diseases targeting this structure [15].

Taken all together, these data suggest that DDR1 is expressed in vascular SMC, and probably in distal tubules and glomeruli at a lower level in physiological conditions in rodents and human. Upon injury, DDR1 expression is triggered in cell types which are more exposed to the aggression.

## Effect of DDR1 inhibition on kidney disease

### Hypertensive nephropathy

In an attempt to unravel the role of DDR1 in renal fibrosis, we induced hypertensive nephropathy in DDR1 KO and WT mice by subcutaneous infusion of angiotensin II for 4 to 6 weeks [13]. In WT mice, this treatment induced sclerotic glomeruli, extracellular matrix deposition, periglomerular and perivascular infiltrates, fibrin deposition in vessel walls and glomeruli, and protein aggregate accumulation in tubular lumen. Despite an

increased and maintained elevated systolic blood pressure of 150 mmHg, DDR1 KO mice displayed a lowered percentage of sclerotic glomeruli and perivascular infiltrate, as well as lower levels of collagen I and IV accumulation. The dramatic decrease of inflammatory cell infiltration in mice lacking DDR1 could not be attributed to a difference in white blood cell composition, as it was similar between both strains in basal condition.

Moreover, while WT mice developed increasing microalbuminuria overtime, DDR1 KO mice exhibited a significantly lower and stable microalbuminuria levels, suggesting that DDR1 deletion tends to stop the progression of the disease more than it delays it.

### **Hereditary type IV collagen disease: Alport's Syndrome**

In an article published in 2010, Gross O. and colleagues [22] have studied the role of DDR1 in a Col4a3 KO mouse model for progressive renal scarring in Alport Syndrome, by crossing them with DDR1 KO mice. They have demonstrated that double KO mice (lacking both Col4a3 and DDR1) lived 47% longer than Col4a3 KO mice without any gender difference. While mice lacking Col4a3 displayed impaired renal function reflected by elevated uremia and proteinuria, and diminution of kidney size due to fibrosis and nephron loss, double KO mice appeared significantly protected. This could be partially explained by reduced foot processes effacement and preserved podocyte architecture. Moreover, double KO exhibited lower glomerular, periglomerular and tubulointerstitial fibrosis associated with decreased connective tissue growth factor and transforming growth factor beta (TGF $\beta$ ) protein expression compared to Col4a3 KO. Finally, T lymphocyte and macrophage infiltrations were decreased in double KO mice in early phases of the disease. However, the diminution of T lymphocyte accumulation in mice deficient in DDR1 was not maintained overtime, as was the case for interleukine-6 (IL-6) mRNA expression. Also, while tumor necrosis factor alpha (TNF $\alpha$ ) and monocyte chemoattractant protein-1 (MCP-1) mRNA expressions were decreased in Col4a3 KO mice heterozygote for DDR1 compared to Col4a3 KO mice, the opposite result was found in double KO mice. The authors proposed that glomeruli from double KO mice were more preserved and thus able to produce more pro-inflammatory cytokines than the ones from other genotypes.

### **Obstructive nephropathy**

Because DDR1 seemed to be a key actor in renal inflammation and fibrosis based on previous reports, our team

studied the role of this receptor in the UO model, a classical model of CKD [14]. In this work, DDR1 KO and WT mice underwent UO and were culled 12 days later, and contralateral kidneys were used as controls. This model induced a 30-fold upregulation of DDR1 expression in the obstructed kidney compared to control. Moreover, macrophage and lymphocyte infiltrations as well as the mRNA expression of pro-inflammatory cytokines such as interferon-gamma, MCP-1, Interleukine-23 and TNF $\alpha$  were significantly reduced in DDR1 KO mice compared to WT. Since DDR1 was notably induced in macrophages in this model, several experiments were conducted on peritoneal macrophages. Results demonstrated that macrophages deficient for DDR1 displayed limited migration capacity towards MCP-1 compared to WT. However, M1/M2 markers were not differentially expressed in WT and KO macrophages and no difference in leukocyte rolling was identified in the mesenteric veins. Consistently with inflammation reduction, mice lacking DDR1 showed reduced Col3a1 and TGF $\beta$  mRNA expressions and exhibited a lower fibrillar collagen accumulation.

### **Nephrotoxic serum-induced glomerulonephritis**

Because we have demonstrated the involvement of DDR1 in the vascular and tubular compartment, we have subsequently studied the role of this protein in a model targeting the glomerular compartment [15]. Injections of sheep serum containing immunoglobulins targeting murine glomerular antigens triggers an immediate inflammatory response leading to glomerular injury (Nephrotoxic serum or NTS-induced glomerulonephritis). In WT mice, NTS intravenous administration induced a 17-fold increase of DDR1 mRNA expression accompanied by elevated systolic blood pressure, increased body weight due to ascites, proteinuria, elevated uremia, crescentic-like formations in glomeruli, fibrin deposition and tubular dilation. All of these parameters were significantly decreased in mice deficient for DDR1. The overall improvement of renal function was reflected by the survival rate which was up to 70% in KO against only 10% in WT 42 days post-injury. Moreover, macrophage infiltration increased overtime in WT, which wasn't the case in KO mice. This result was mirrored by the decreased mRNA expressions of pro-inflammatory mediators such as interleukin-1beta, MCP-1, intercellular adhesion molecule and vascular adhesion molecule-1 in DDR1 KO. Fibrillar collagen deposition was induced in WT mice as shown by sirius red staining and the elevated mRNA levels of Col1a2, Col3a1, Col4a3 and TGF $\beta$ . These parameters were significantly lower in DDR1 KO mice. Finally, preventive

administration of oligodeoxynucleotide antisense (ODN AS) targeting DDR1 successfully decreased its expression and blunted the elevation of proteinuria, uremia and body weight. This treatment also protected podocyte structure as shown by the preservation of nephrin expression, a marker of foot processes integrity.

### **Remnant kidney model**

In a recent publication, the role of DDR1 has been studied in the remnant kidney model, or 5/6 nephrectomy, in DDR1 KO mice [23]. The authors have demonstrated that the level of glomerular injury and the mesangial sclerosis index was significantly lower in mice lacking DDR1 compared to their WT littermate. Pico Sirius, Masson's trichrome staining and collagen IV immunostainings have also showed a decreased collagen accumulation within DDR1 KO glomeruli. Finally, this protection was mirrored by the albumin to creatinine ratio which was significantly higher in WT than in mice deficient for DDR1.

### **Therapeutic inhibition of DDR1 expression**

The above-mentioned studies have shown a major role of DDR1 in inflammation and fibrosis induced in five models of experimental nephropathies [13–15,22,23]. The involvement of DDR1 in renal diseases and its limited physiological functions make it an interesting therapeutic target. For that reason, we designed curative protocols in two different models of CKD: NTS-induced glomerulonephritis and UUO [16]. WT mice were injected repeatedly with ODN AS targeting DDR1 or non-specific scrambled (SCR), or saline buffer after the onset of the disease. In the NTS model, injections started either during an early phase of the disease, or during an intermediate phase. In the UUO model, injections started in an early phase. In both models, AS administration successfully decreased DDR1 mRNA and protein expressions. As result, AS-treated mice exhibited decreased uremia, proteinuria, and body weight intake compared to SCR. Histological alterations such as crescentic-like formations, glomerulosclerosis and tubular dilation were drastically decreased in mice treated during the early phase of the pathology. Mice treated later were also protected but to a lesser extent. The same trend was observed regarding the inflammation influx represented by F4-80 and CD3 $\epsilon$  staining, as well as the fibrillar collagen accumulation and mRNA levels of Col1a2, Col3a1 and TGF $\beta$ . These results have shown the high efficiency of DDR1 inhibition in glomerular disease even if the treatment was administered at a later stage of the pathology. In the UUO model, AS-treated mice displayed a

reduction of tubular dilation, inflammation and interstitial collagen accumulation demonstrating that the protection was not model-dependent.

Taken together, these results constitute a « proof of concept » that DDR1 is a promising therapeutic target and that its inhibition can at least stop, or reverse the progression of CKD.

### **Discussion**

DDR1 has been widely studied in different kind of diseases and a variety of cancers. Its singular ability to bind collagens associated to its tyrosine kinase activity make it an interesting receptor. In basal conditions, DDR1 is expressed in vascular SMC in kidney [12–17]. Its expression has also been described in distal tubules and glomeruli but this varies depending on the specie and the antibody [12–17,19].

In pathological settings, DDR1 de novo or over-expression seems to be induced in the cell type most targeted by the renal injury: renal vessels and mesangium in hypertensive nephropathy [13], podocytes in a model of Alport's Syndrome [22] and in the NTS-induced glomerulonephritis [15], hypertrophic glomeruli in the remnant kidney model [12], and mainly tubules and macrophages in the UUO model [14,16]. The deleterious effect of DDR1 has been demonstrated in all of these models by using genetic or pharmaco-genetic inhibition [24]. However, the mechanisms driving DDR1 expression and activation, and the downstream pathways mediating its pro-inflammatory and pro-fibrotic effects are not well defined.

Several studies have proposed the involvement of p53, XRCC3, the DDR2/ERK pathway and DDR1 itself, through the activation of the Ras/Raf/ERK pathway, in DDR1 up-regulation [24]. Other investigators have identified a binding site for Zeb-1 on DDR1 promoter as well as two microARNs able to down-regulate DDR1 expression. However, the mechanisms driving DDR1 transcriptional regulation in healthy and diseased kidney are poorly understood. Besides, little is known about the mechanism(s) leading to DDR1 shedding following collagen binding [10,11]. The cleaved form of DDR1 is detectable in kidney as evidenced by the presence of several proteins with smaller molecular weights revealed on western blots performed on membrane and whole kidney lysates [12]. Whether the shedded extracellular domain of DDR1 plays a role in the pathophysiological processes involved in nephropathies has yet to be determined.

In a report published in 2002, Curat CA and colleagues [18] demonstrated an increased proliferation and decreased adhesion of DDR1 KO mesangial cells in culture. This result was in contradiction with previous data indicating that vascular SMC lacking DDR1 displayed

decreased growth rate [8]. It has also been demonstrated, in two renal cancer cell lines, that collagen I-induced DDR1 expression promotes migration and epithelial-to-mesenchymal transition, while treatment with a siRNA targeting DDR1 has the opposite effect [25]. In a recent study, Borza C. and colleagues [23] compared DDR1 KO mesangial cells to a mesangial cell line lacking this gene but stably reconstituted with the human DDR1b. Collagen IV expression was induced in cells expressing DDR1 compared to KO and was triggered after collagen I treatment. By using two different mutants disabling either collagen binding or the tyrosine kinase activity, the authors showed that this effect was both ligand and kinase dependent. Finally, collagen IV production could be inhibited by an ATP-competitive small molecule targeting DDR1, showing that DDR1 activation directly regulate collagen IV production in mesangial cells.

The emergence of selective inhibitors of DDR1 is of particular interest from a therapeutic point of view [26–28]. Published studies have demonstrated the effect of DDR1 inhibitors on cancer cells invasiveness *in vitro* and *in vivo* but they have never been tested in experimental kidney disease [26,28].

Clinical data supporting the role of DDR1 in human CKD are limited. In 2010, Hahn W-H and colleagues [29] identified several single nucleotide polymorphisms of the DDR1 gene associated with childhood IgA nephropathy, the most commonly occurring form of chronic glomerulonephritis. In addition, we have demonstrated a *de novo* expression of DDR1 in glomerular cells of patients suffering from glomerulopathies such as lupus nephritis and Goodpasture's syndrome [15]. A thorough study of DDR1 expression in various human kidney diseases has yet to be performed. Unravelling the mechanisms surrounding DDR1 expression and activation would allow the further understanding of renal pathophysiological processes and would pave the way towards the development of new therapeutic strategies against CKD.

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### ORCID

Aude Dorison  <http://orcid.org/0000-0002-8329-8767>PhD

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