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The Role of Discoidin Domain Receptor 1 in Inflammation, Fibrosis and Renal Disease

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Chronic kidney disease · Fibrosis · Inflammation · Target of therapy

Abstract
Discoidin domain receptors (DDRs) are a family of 2 non-integrin collagen receptors, DDR1 and DDR2, which display a tyrosine kinase activity. They are mainly expressed during embryonic development and their role during adulthood is very limited. DDR1 has been widely studied in several types of cancers, in atherosclerosis and fibrosis, but also in chronic kidney disease (CKD). This review focuses on the role of DDR1 in chronic nephropathies and on the effect of its deletion in the pathological processes involved in renal disease progression. DDR1 was shown to be de novo expressed in several models of experimental CKD. Its genetic or pharmaco-genetic inhibition led to the preservation of renal structure and function, and to decreased inflammatory influx and fibrosis. Furthermore, delayed pharmaco-genetic inhibition of DDR1 led to significant protection in models of renal disease. These results demonstrate the involvement of DDR1 in inflammatory and fibrotic processes occurring during CKD and the beneficial effect of its inhibition. Thus, DDR1 could be an interesting therapeutic target to treat renal pathologies.

Introduction

Discoidin domain receptors (DDRs) are a family of 2 non-integrin collagen receptors, DDR1 and DDR2. They display a tyrosin kinase activity and were discovered in the early 1990s [1]. However, their ligands remained unknown until 1997, when 2 different research groups identified collagens as their physiological ligands [2, 3]. The gene coding for DDR1 is mapped on chromosome 6 (6p21.3) in human and chromosome 17 in mouse, whereas the DDR2 gene is located on the chromosome 1 in both species (1q23.3) [4]. DDR1 gene comprises 17 exons that are alternatively spliced to form 5 different isoforms, DDR1a to DDR1e, while only one isoform for DDR2 has been identified yet [5].

DDR1 and DDR2 share a similar structure. They have 2 globular domains: an N-terminal discoidin domain and a discoidin-like domain. Both these domains are linked to each other and are highly conserved between the DDRs. Following these domains, there is a unique transmembrane region continuing with a long cytosolic juxtamembrane domain and a catalytic tyrosine kinase domain followed by a very short C-terminal tail [6]. DDR1 isoforms are identical in their extracellular and transmembrane region. The alternative splicing induces modifications in the intracellular catalytic domain leading to length modification (DDR1a to DDR1c) and kinase inactivation

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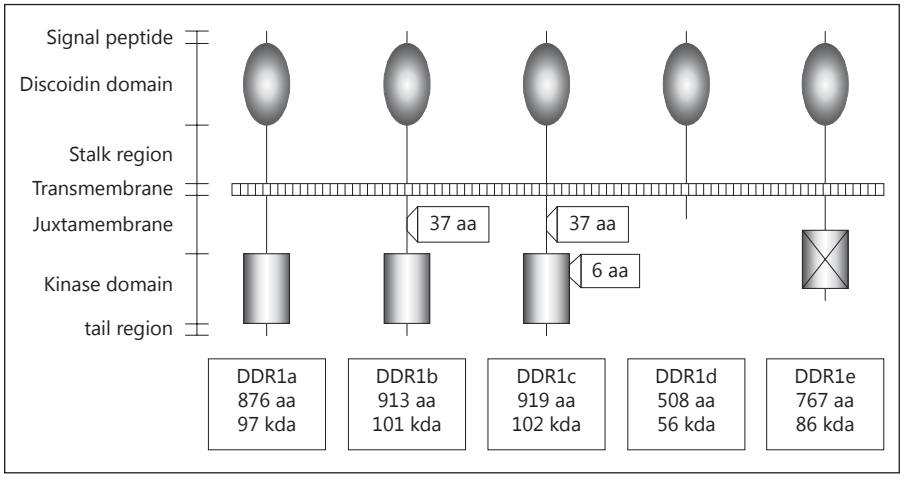

Fig. 1. The protein structure of DDR1 isoforms [5].

(DDR1d and DDR1e; Fig. 1). The most frequently expressed isoforms are DDR1a and DDR1b [5]. DDRs can bind native fibrillar collagens I and III with similar affinities [2, 3] but differ in their binding to non-fibrillar collagens. For instance, DDR1 can bind the collagens type IV, VIII and XV, whereas DDR2 has an increased affinity to collagen II and X [2, 3, 7–10]. DDRs binding sites have been mapped and are located in the globular discoidin domain [6].

The process leading to DDRs activation differs from the processes of other tyrosine kinase receptors. In basal conditions, DDRs are expressed as dimers at the membrane. After collagen binding, the auto-phosphorylation of the catalytic domains occurs slowly and can be maintained for several days depending on the cell type [2, 3]. Collagen binding has been shown to promote DDR1 cleavage in the extracellular juxtamembrane region releasing a soluble 54kDa DDR1 extracellular domain [11]. The exact molecular mechanism by which the collagen binding induces DDRs phosphorylation remains unknown [12]. In contrast, several downstream pathways have been demonstrated or suggested in the literature. A presentation of these pathways is provided in Figure 2.

Physiological Role of DDRs

DDRs are expressed during the early embryonic development in different tissues in human and mice. While DDR2 is found in cells of the connective tissue, DDR1 is mainly present in epithelial and smooth muscle cells (SMCs) [1]. For instance, DDR1 has been described in bronchial epithelium, keratinocytes, colon epithelium, liver, cornea, vascular SMCs in humans, as well as in the developing neuroectoderm, mammary glands, brain, distal tubule, podocytes and SMCs in mice [13, 14]. However, no systematic analysis of cellular distribution of DDRs was performed.

Both DDRs play an important role during embryonic development. DDR1 is involved in organogenesis, whereas DDR2 participates in bone growth in mice and humans. Their function was initially studied, thanks to the generation of knock-out (KO) mice for DDR1 and DDR2, respectively [15, 16]. DDR1 KO mice were smaller than their wild type (WT) littermates on the mixed genetic background 129/Sv-ICR and 129/Sv-C57/B6. Moreover, female mice lacking DDR1 displayed multiple reproductive defects including impaired blastocyst implantation leading to infertility. This phenotype was associated with abnormalities of the mammary gland epithelium inducing a deficient lactation process [15]. DDR1 KO mice also exhibited abnormalities in the inner ear architecture leading to impaired audition [17]. In kidney, an initial study reported a thickening of the glomerular basement membrane, which did not affect the renal function, since uremia was at the normal range [13]. In another study, the same group of investigators reported that <2% of glomeruli presented this abnormality, and that it appeared only in aged mice [18]. Mice lacking DDR2 displayed dwarfism with short long-bones and a shorter snout due to reduced chondrocyte and osteoblast proliferation and differentiation [16, 19, 20].

Despite their role during embryogenesis, the physiological function of DDRs during adulthood is rather negligible. In certain conditions, they regulate the expression and activity of matrix metalloproteinases and proinflammatory cell migration [12].

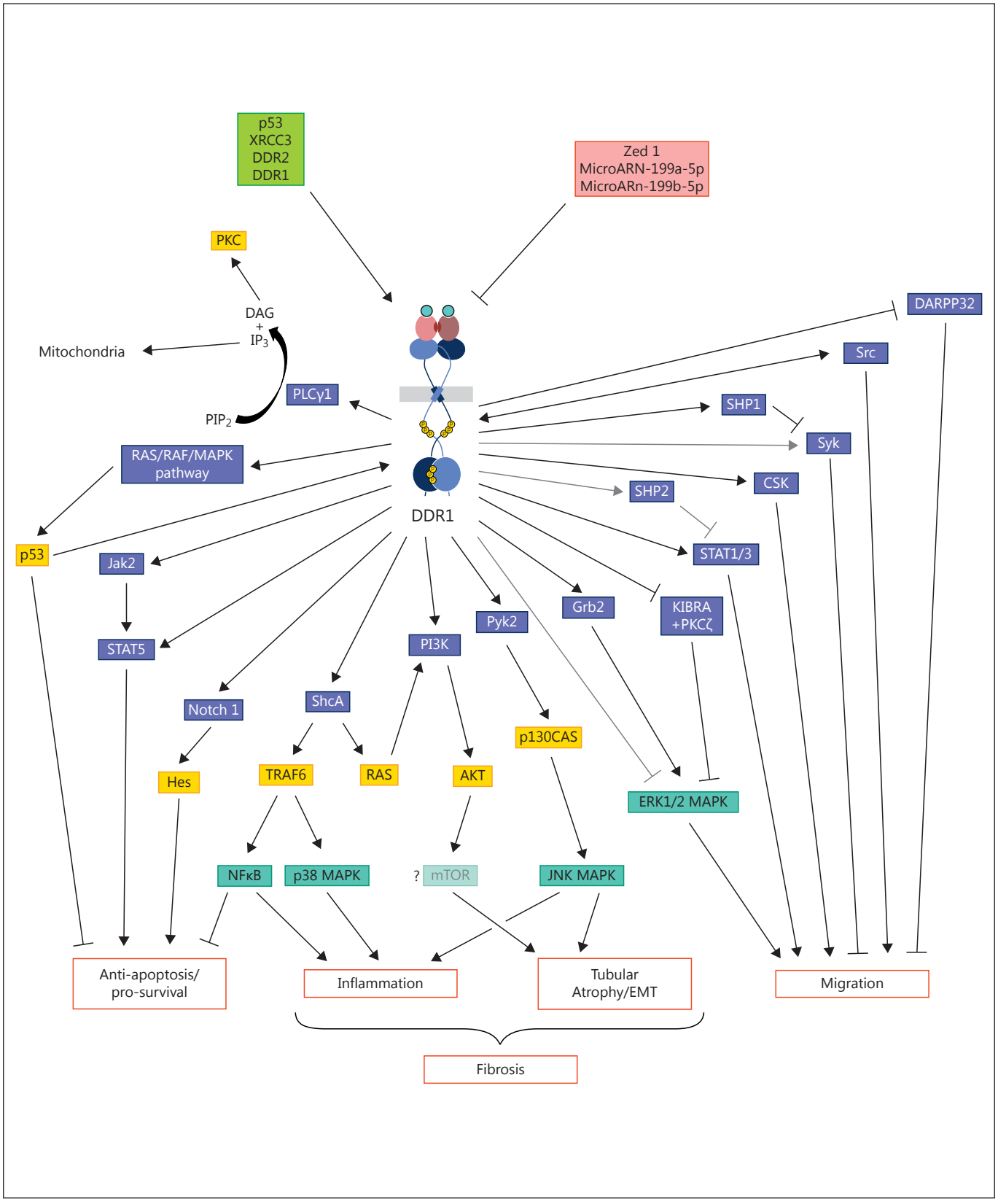

Fig. 2. Scheme of demonstrated and presumable DDR1 up-stream and down-stream pathways [12, 50].

DDR1 in Disease

As is the case with other tyrosin kinase receptors, DDR1 is de novo activated in a number of pathologies to participate in proliferation, inflammation and fibrosis. In this review, we present briefly the literature concerning the role of DDR1 in cancer, atherosclerosis and fibrosis and then we present the recent developments linking DDR1 activation to the progression of CKD.

Cancer

DDR1 overexpression has been widely described in several cancer cell lines and in cancer patients. Indeed, its expression has been found increased in breast [1], ovarian [21], brain [22], oesophagus [23] and lung cancer [1] and in acute lymphocytic leukemia [24]. These observations suggest an important involvement of DDR1 in the development and the progression of tumors. It appears that the importance of the role of DDR1 depends on the cancer type and stage [25]. Some studies have demonstrated that DDR1 overexpression increased tumorigenesis and was correlated with a bad prognosis [26]. A recent study has shown that DDR1 was an interesting biomarker in renal cancer and that it promoted the epithelial to mesenchymal transition in cancer cells [27]. DDR1 expression was also enhanced in the early phases of KRAS-driven lung adenocarcinoma and its inhibition in vivo protected mice in an experimental model of this disease [28]. However, the molecular mechanisms downstream DDR1 activation in cancer cells are mostly unknown.

Atherosclerosis

DDR1 KO mice exhibited decreased neointimal formation compared to their WT littermates following mechanical injury of the carotid arteries [9]. This protection was attributed to the low collagen accumulation associated with the decreased proliferation, migration and MMP2 production in vascular SMCs of DDR1 KO mice [9, 29]. Furthermore, DDR1 involvement in atherosclerosis was studied in low-density lipoprotein receptor KO (Ldlr KO) mice. Franco et al. [30] demonstrated that despite a surprising increase in fibrillar collagen accumulation in atherosclerotic plaques of DDR1/Ldlr KO mice at early stages, they exhibited a 50–60% reduction in the atherosclerotic lesion area. Thus, the authors proposed that the decreased lipid accumulation associated with the increased extracellular matrix (ECM) production prevented the rupture within plaques of DDR1/Ldlr KO mice [31]. Additional studies showed the prominent proinflammatory effect of DDR1 in atherosclerosis. Indeed, the macrophage infiltration was significantly decreased within atherosclerotic plaques of DDR1/Ldlr KO mice. Moreover, target deletion of DDR1 in bone marrow cells led to a significant delay in the development of atherosclerosis, while macrophages from DDR1 KO mice displayed reduced adhesion on collagen type IV and decreased expression of monocyte chemoattractant protein 1 (MCP-1) [32]. Taken together, these results demonstrate an important involvement of DDR1 in the proinflammatory and profibrotic processes associated with atherosclerosis.

Fibrosis

In a bleomycin-induced lung injury model, DDR1 was de novo expressed in injured epithelial cells to regulate inflammation and fibrosis. Compared to their WT littermates, DDR1 KO mice exhibited less macrophage and lymphocyte infiltration, less fibrotic scars and inhibition of the p38 MAPK pathway driving inflammation in this model [33]. These results are in agreement with another study showing that the inhibition of the p38 MAPK pathway was able to diminish inflammation and fibrosis in the bleomycin-induced pulmonary fibrosis model [34]. In addition, DDR1 is expressed in the human bronchial epithelium during disease, and several in vitro experiments imply that DDR1 is involved in the damage of bronchial cells [35, 36]. These studies suggested that DDR1 could play an important role in idiopathic pulmonary fibrosis mediating the creation of permanent pulmonary epithelial lesions.

DDR1 has also been studied in skin fibroblasts during fetal healing in developing rat embryos. However, DDR1 expression was reduced during later phases suggesting that DDR1 could be involved in repair processes independently from ECM regulation and formation [37].

DDR1 in Renal Physiopathology

Hypertensive Nephropathy

We were among the first investigators interested to examine if DDR1 can be involved in the mechanisms of progression of chronic kidney disease (CKD). We used a model of hypertension-induced renal disease, and we postulated that if DDR1 is involved in the fibrogenic pro-

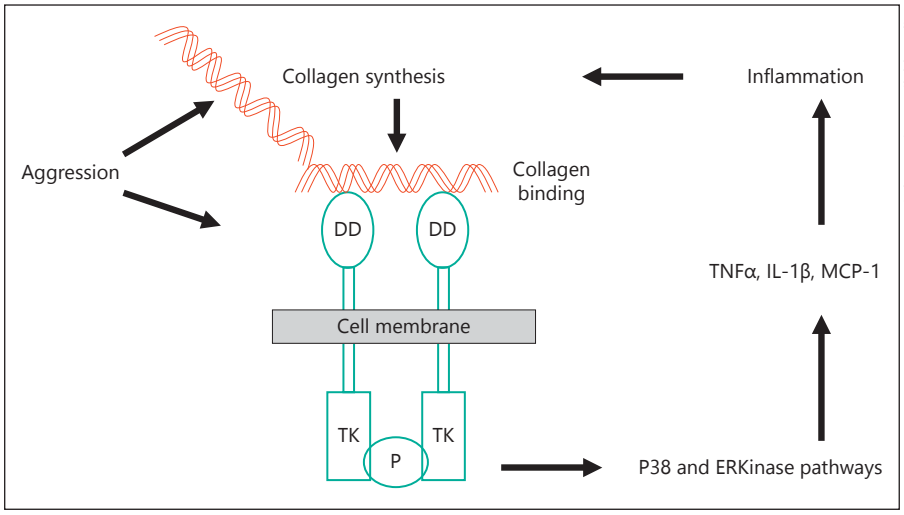

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Fig. 3. DDR1 activation induces an inflammatory response, which further increases collagen synthesis and ultimately leads to the amplification of renal inflammation, exaggerated accumulation of fibrosis and loss of renal function.

cess acting as a collagen receptor, then mice lacking functional DDR1 should be protected against renal fibrosis compared to WT animals, and this protection should be independent of blood pressure levels. Thus, angiotensin II (Ang II) was administered for 4–6 weeks to DDR1 KO mice and their WT littermates, and blood pressure, and renal function and histology were analyzed [38]. In response to hypertension, DDR1 was de novo expressed in vascular SMCs and mesangial cells of WT animals. This observation was associated with marked perivascular inflammation, arteriolosclerosis and glomerulosclerosis. DDR1 KO, exposed to the same degree of hypertension, was protected against inflammation and renal fibrosis. They exhibited a lower level of perivascular T lymphocyte and macrophage infiltration, and a decreased accumulation of types I and IV collagens. The histological preservation of renal structure was reflected on parameters of renal function such as micro-albuminuria [38].

Since DDR1 was not expressed in lymphocytes or macrophages in this model of hypertensive nephropathy, we proposed the following mechanism of action: Ang II increases DDR1 expression in renal vessels and mesangial cells probably through a cellular mechanism involving endothelial cell stress. In parallel, Ang II directly induces the abnormal expression of collagen types I, III and IV in renal microvessels and glomeruli [39]. As a result, collagens bind to DDR1 leading to its activation and phosphorylation. This activation of DDR1 stimulates proinflammatory pathways, such as p38 MAPK pathway or nuclear factor κB, inducing cytokines synthesis. Finally, proinflammatory cytokines further enhance inflammatory cell infiltration, ECM synthesis and DDR1 expression (Fig. 3). This scheme proposes DDR1 as an amplifier of the initial renal vascular lesion by creating a positive deleterious feedback between inflammation and collagen production, which leads to the development and progression of CKD.

Hereditary Kidney Diseases: Alport's Syndrome

Other investigators studied the role of DDR1 in kidney of mice lacking the α3 chain of type IV collagen (Col4a3), mimicking the Alport's syndrome [18]. The double KO mice for DDR1 and Col4a3 displayed increased survival rate and preserved renal function (decreased proteinuria and blood urea nitrogen). The authors attributed this protection to a decrease of renal inflammation and fibrosis through the inhibition of interleukine-6, nuclear factor κB, connective tissue growth factor and transforming growth factor β (TGFβ). Of interest, the expression of DDR1 in the Alport mice was induced in podocytes, which are the cells involved in this renal disease [18].

Tubular Obstructive Nephropathy

Since interstitial injury, cellular infiltration and ECM deposition are considered the key steps in the progression of CKD, our team studied the role of DDR1 in the unilateral ureteral obstruction (UUO) model using mice deficient in DDR1 expression [40]. In this model, DDR1 was several fold upregulated at both mRNA and protein expression levels. Interestingly, DDR1 induction was localized in tubules, interstitium and infiltrating macrophages. Proinflammatory cytokines such as interferon γ, MCP-1, interleukin-23 and tumor necrosis factor α, were significantly increased, as well as TGFβ and Col3a1 expression [40]. Again, DDR1 KO mice were protected showing lower perivascular inflammation (macrophages and T lym-

phocytes) and less interstitial fibrosis. Experiments performed with Boyden chambers coated with collagen IV [32, 40] showed that macrophages freshly isolated from mice lacking DDR1 expression exhibited a reduced capacity of migration compared with macrophages isolated from WT animals. This observation suggests that DDR1 expression and activation in macrophages are essential for efficient migration and indicates the role of DDR1 in mediating interstitial lesions associated with macrophage infiltration in kidneys.

Nephrotoxic Serum Glomerulonephritis

In this model, also called anti-GBM (Glomerular Basal Membrane), there was an early and progressive induction of DDR1 expression in podocytes and proximal tubular cells [41]. Just as it was with the previous models of renal disease, DDR1 KO mice were protected compared to their WT littermates. Indeed, they exhibited blunted proteinuria and uremia, less crescent-like formations and fibrin deposition, decreased macrophage infiltration and lower peri-glomerular and tubulo-interstitial fibrosis. The reduction of the inflammatory influx was accompanied by decreased levels of proinflammatory mediators, such as interleukin-1β, MCP-1, vascular cell adhesion molecule-1 and intercellular adhesion molecule. Moreover, Col1a2, Col3a1, Col4a3 and TGFβ levels were lowered, as it was the case in the UUO model. In addition, the lifespan of mice lacking DDR1 was significantly extended in comparison with WT mice [41].

To further demonstrate that the protection was due to DDR1 inhibition, we designed a complementary study using antisense oligodeoxynucleotides (AS) targeting DDR1 in a preventive approach, since the AS administration started 3 days before the onset of the disease. The preventive inhibition of DDR1 in this model led to the same protective effect than what we observed with DDR1 KO mice [41]. The strategy of using antisense oligonucleotides provided a first proof of concept that DDR1 can be a potential target for therapy in renal disease because it avoids an indirect renal or vascular effect of DDR1 gene deletion during the embryonic development.

DDR1 as Target of Therapy

The above-mentioned studies have shown a major role of DDR1 in the inflammatory response and fibrogenesis in 4 different models of experimental nephropathy. They demonstrated that DDR1 is de novo expressed by injured epithelial, inflammatory or mesangial cells after a mechanical, toxic and/or immunological aggression. The neo-expression and activation of DDR1 trigger inflammation, fibrosis and the migration of DDR1-overexpressing cells [18, 38, 40, 41]. However, the KO mice or the AS administration before the onset of the renal disease is a form of a preventive approach. Thus, subsequent experiments were performed to demonstrate whether or not DDR1 blockade can be used efficiently as a therapy approach. To test this, curative protocols were applied in 2 different models of CKD, NTS-induced glomerulonephritis and UUO [42]. WT mice were injected every 48 h either with AS targeting DDR1, non-specific scrambled oligodeoxynucleotides or saline, after the onset of the disease: from day 4 (early phase) or day 8 (intermediate phase), or from day 2 after the ligation, in the NTS or UUO protocols, respectively. In both models, DDR1 mRNA and protein expressions were 50% decreased after AS administration. As with the preventive AS administration, AS-treated mice displayed lower proteinuria, body weight intake and uremia levels than mice receiving non-specific scrambled at the end of the treatment. Crescentic-like formations, glomerulosclerosis and tubular dilation were markedly decreased in mice receiving AS from day 4, while the protection was still significant, but to a lesser extent when the treatment was started from day 8. The early inhibition of DDR1 blunted the inflammation influx, as well as the fibrillar collagen accumulation and the expressions of Col1a2, Col3a1, and TGFβ. When DDR1 was inhibited at the late phase of disease, the macrophage infiltration associated with tumor necrosis factor α and MCP-1 and fibrillar collagen deposits were significantly decreased as well. These results have shown that DDR1 inhibition after the onset of the glomerular disease efficiently protected the animals even if the treatment was administered at a later stage of the pathology [42]. Similar results were obtained with the UUO model: the delayed inhibition of DDR1 preserved the deterioration of renal structure as AS administration blunted tubular dilation, macrophage infiltration and interstitial collagen accumulation showing that DR1 blockade-induced protection was not model-dependent [42]. These results provide the proof of concept that DDR1 is an interesting therapeutic target and that its inhibition can stop or reverse the progression of CKD.

Discussion: What Is the Future of the Pharmacological Inhibition of DDR1?

Because of its particular characteristic of being a non-integrin collagen receptor displaying a tyrosin kinase activity, DDR1 has raised the interest of several research

groups working on the field of fibrosis. The surprise future of DDR1 is that in addition to the fibrotic action, it is also strongly involved in the inflammatory process. In the case of renal pathology, it has been demonstrated that DDR1 is induced locally in cell types that are involved in the response to the renal injury: renal vessels and mesangium in hypertension [38], podocytes in a model of Alport's syndrome [18] and in the NTS-induced glomerulonephritis [41, 42], and tubules and macrophages in the UUO model [40, 42]. It was possible to display the major role of DDR1 in the progression of inflammation and fibrosis in these models of CKD by using mice lacking DDR1. However, clinical data supporting the role of DDR1 in human CKD are rare. In 2010, Hahn et al. [43] pointed out an association between several DDR1 polymorphisms and the progression of IgA nephropathy in children. In addition, we have shown in a limited number of patients' biopsies that DDR1 is expressed in glomeruli in different glomerulopathies, such as lupus nephritis and Goodpasture's syndrome [41, 42]. A thorough study about the expression of DDR1 in human kidney disease is yet to be conducted.

The results from the animals lacking DDR1 receptors combined with the results of AS administration clearly showed the potential of DDR1 blockade as a target of therapy. Some inhibitors of tyrosine kinase receptors with a selectivity factor also for DDR1, such as imatinib or nilotinib, have been tested with mixed results. Imatinib gave encouraging results in several models of experimental CKD [44]. However, it displays some unpleasant adverse effects (such as nausea, diarrhea, periorbital edema or muscle cramps), probably due to the non-selective inhibition of tyrosine kinase receptors, which results in the epithelial toxicity spread in several tissues. Nilotinib was tested in the model of 5/6 Nephrectomy with promising results [45]. Dasatinib, bosutinib, bafetinib and ponatinib can also bind the kinase domain of DDRs [46, 47]. However, their lack of selectivity will probably result in secondary effects similar to those of imatinib.

Recent investigations have reported the synthesis of specific DDR1 and/or DDR2 inhibitors tested in vitro and/or in vivo [28, 48, 49]. Kim et al. [48] created 2 specific inhibitors of DDRs, DDR1-IN-1, and DDR1-IN-2 derived, respectively, from nilotinib and imatinib. DDR1-IN-1 displayed a better selectivity than DDR1-IN-2 but was less efficient to inhibit cancer cell lines proliferation. In another study, Gao et al. [49] synthesized a compound that inhibited DDR1 selectively – the compound 7rh derived from ponatinib. It exhibited a specificity for DDR1 twentyfold higher than DDR2 and sixtyfold higher than the chimeric protein breakpoint cluster region-abelson kinase. The screening of a large kinase set resulted in an inhibitory effect of 35% for only 1% of tested proteins. In addition, this compound inhibited DDR1 signaling in cells derived from a non-small cell lung carcinoma, thereby reducing their invasiveness. Finally, this compound has been successfully used in vitro and in vivo to inhibit DDR1 in a murine model of KRAS-driven lung adenocarcinoma [28].

The development of these specific blockers will allow a broader investigation of DDR1 signaling in vitro and in vivo. Still, several questions regarding the mechanisms of action of DDR1 remain unanswered, such as the identity of the signal triggering DDR1 de novo expression and/or activation, whether DDR1 is activated only by collagen binding or if it can be transactivated by other phosphorylated receptors (as is the case with other tyrosine kinase receptors), the existence and consequences of DDR1 shedding in vivo and the fate of DDR1 receptor after its phosphorylation.

The fact that DDR1 is silenced during adulthood and is re-activated during pathological processes is of particular interest. The literature does not contain any information about the role of DDR1 in embryonic kidney development. However, the observation that the DDR1 KO mice display normal renal function and structure, at least until 12 month-old, implies that the impact of DDR1 in renal development is negligible.

From the point of view of renal physiopathology, the questions regarding the identification of the signal inducing DDR1 expression in kidneys and the direct promotion of renal disease by DDR1 activation are important. Indeed, very little is known about the mechanisms regulating DDR1 transcription in general as in the context of renal pathology. 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 upregulation. Other investigators have identified a binding site for Zeb 1 on DDR1 promoter as well as 2 microARNs able to downregulate DDR1 expression [12] (Fig. 2). Considering the lack of data concerning DDR1 transcriptional regulation, we believe that unravelling these mechanisms would enable the further understanding of renal physiopathological processes and would pave the way towards the development of new therapeutic strategies against CKD.

Disclosure Statement

The authors have no conflicts of interest to declare.

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