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Discoidin domain receptor-1 and periostin: new players in chronic kidney disease

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ABSTRACT

The incidence and prevalence of chronic kidney disease represents an important problem for public health. In renal diseases, the main histologic alterations derive from the development of renal fibrosis which results from the loss of the balance between pro- and anti-fibrotic factors. Tyrosine kinase receptors (RTKs) and matricellular proteins (MPs) are nowadays studied as potential modulators of renal injury. RTKs regulate cell cycle, migration, metabolism and cellular differentiation. Discoidin domain receptor-1 (DDR-1) is an RTK that has been extensively studied in cancer, and lung and renal diseases. It modulates inflammatory recruitment, extracellular matrix deposition and fibrosis; in renal diseases, it appears to act independently of the underlying disease. MPs regulate cell-matrix interactions and matrix accumulation, cellular adhesion and migration, and expression of inflammatory cells. Periostin is an MP, mainly studied in bone, heart, lung and cancer. Several studies demonstrated that it mediates cell-matrix interactions, migration of inflammatory cells and development of fibrosis. Recently, it has been reported in several nephropathies. In this review, we discuss the potential pathological roles of DDR-1 and periostin focussing on the kidney in both experimental models and human diseases.

Keywords: discoidin domain receptor-1, matricellular proteins, periostin, renal fibrosis, tyrosine kinase receptors

INTRODUCTION

Chronic kidney disease (CKD) represents a major problem for public health. It affects up to 10% of the general population with a prevalence and incidence that has increased worldwide over the past 25 years and has almost doubled in both the USA and Europe [1]. Diabetes and high blood pressure are the major causes of CKD, followed by glomerulonephritis. Independent of the underlying cause, the pathogenesis of CKD is characterized by the progressive impairment of glomerular, tubulointerstitial and vascular compartments. Chronic exposure of these structures to pathogens leads to the development of glomerulosclerosis, interstitial fibrosis, tubular atrophy and vascular sclerosis.

For CKD patients, dialysis and renal transplantation are the only effective therapies. Apart from drugs targeting the renin–angiotensin system (RAS), which are only partially effective, there are no drugs able to reduce or reverse fibrotic processes during kidney diseases.

This review consists of three parts: in the first, recently published data about novel mediators of renal fibrosis are discussed; in the second and third ones, the role of tyrosine kinase receptors and matricellular proteins (MPs) in both renal and other diseases are briefly presented, focussing mainly on DDR-1 and periostin, respectively.

OLD AND NOVEL MEDIATORS OF RENAL DAMAGE

Development of renal fibrosis is characterized by accumulation and deposition of extracellular matrix (ECM) and microvascular rarefaction. The mechanisms underlying these processes result from the loss of the correct balance between pro- and anti-fibrotic factors (Figure 1) [2]. The main acknowledged mediators of renal fibrosis are angiotensin II (Ang-II), endothelin-1, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor and the

FULL REVIEW

inhibitor of type 1 plasminogen activator. Among them, Ang-II, TGF-β and PDGF have been better studied and characterized.

Overexpression of Ang-II, typical in most renal diseases, is directly correlated with an increase in the expression of other pro-fibrotic factors, such as TGF-β, collagen I, collagen IV and matrix metallopeptidase-2 and 9. Drugs targeting AT II action or production have a protective effect in both kidney and heart diseases, since they inhibit the progression of CKD and reduce cardiovascular risk in CKD patients. TGF-β is also a major pro-fibrotic factor. Its overexpression promotes ECM synthesis and deposition and, at least *in vitro*, epithelial–mesenchymal transition (EMT). The protective effect of its blockage has been demonstrated by several groups in different experimental models of nephropathies [3]. Pirfenidone is a recently developed anti-TGF-β drug. Whereas its precise mechanism of action is not totally understood, it exhibits both anti-fibrotic and anti-inflammatory effects. In detail, it reduces fibroblast proliferation and the expression of TGF-β in experimental models; in patients with lung and kidney fibrosis, it showed clear anti-fibrotic properties. Moreover, it is able to reduce the production of inflammatory mediators such TNF-α and interleukin-1 [4]. Concerning kidney diseases, the drug was tested in focal and segmental glomerulosclerosis and in diabetic nephropathy with encouraging results [5].

Another important pro-fibrotic factor is PDGF, which is expressed in most renal cells during development and after injury [6] and modulates cell proliferation and migration, ECM accumulation, production of pro- and anti-inflammatory mediators and tissue permeability. PDGF receptors have tyrosine kinase activity and, similar to the majority of this kind of receptors, upon ligand binding are autophosphorylated. PDGF inhibitors have been developed and used to treat gastrointestinal and breast cancers, but unfortunately all of them exhibit limited selectivity for PDGF [7].

Among other anti-fibrotic factors, bone morphogenic proteins (BMPs), tissue plasminogen activator and hepatic growth factor (HGF) are the most studied. BMPs, especially BMP-7, and HGF act as natural TGF-β antagonists by blocking Smad 2/3 nuclear translocation in interstitial fibroblasts. Unfortunately, the encouraging results obtained from experimental models were not reproduced in clinical trials [8].

TYROSINE-KINASE RECEPTORS AND DDR-1

Receptors with tyrosine kinase activity (RTKs) are transmembrane receptors with intrinsic, ligand-stimulable tyrosine kinase activity. Insulin receptor, epidermal growth factor receptor (EGFR), PDGFR and fibroblast growth factor receptors (FGFRs) are part of this group of receptors. They regulate cell cycle, migration, metabolism and cellular differentiation both during embryogenesis and in adult life.

A typical RTK comprises three domains: (i) extracellular, the binding site of the ligands; (ii) transmembrane (22–26 amino acids), with anchorage functions; (iii) intracellular, the signal transduction domain, composed of a juxtamembrane region, a tyrosine kinase catalytic domain and a carboxyl-terminal region. Usually, the binding of the ligand is followed by dimerization of the receptor, autophosphorylation and, finally, the transduction of the signal and the activation of several intracellular pathways including MAP kinases (Erk1/2, Jnk, p38, Rrk5) and PI3k/AKT [9].

DDR-1 is an RTK. In humans, the DDR-1 gene is localized on chromosome 6, in the region 6p21.3 [10]. Compared with the other RTKs, it has a longer juxtamembrane domain and a unique activation pattern that takes place several hours after the initial stimulation. DDR-1 is activated by several types of collagen including collagen I–VI and VIII in its native, triple-helical form; due to alternative splicing in the intracellular domain, five isoforms have been identified (a- to -e) [11]. Each isoform seems to have a distinct and specific biological role. For example, DDR-1b protein is the predominant isoform expressed during embryogenesis, whereas the a-isoform is commonly found in several human mammary carcinoma cell lines. As with most RTKs, MAP kinase and PI3 pathways are the downstream effectors of DDR-1 (Figure 2).

Generation of the DDR-1 knock-out mice led to the determination of the biological role of DDR-1 in morphogenesis, differentiation and proliferation in several organs. Initial reports stated that DDR-1 KO mice are smaller than wild-type mice, and that females are not fertile due to defects in blastocyst implantation and are unable to produce milk [12]. However, these initial observations were not confirmed in subsequent studies using KO mice with a stable genetic background.

In human atherosclerosis, the activation of the receptor seems to be implicated in the induction of MMP1 and MMP2 expression, therefore modulating ECM accumulation [13]. DDR-1 has been widely studied in cancer and shown to be overexpressed in many types of cancers including brain [14], ovarian [15], liver [16], pancreatic [17], prostate [18] and colon [19] cancer. In these cancers, DDR1 overexpression, which mediates proliferation and the metastatic process, correlates with the progression of the disease, therefore representing a potential prognostic marker [20]. In haematologic disorders, anomalies in the expression of DDR-1 were described in acute lymphoblastic leukaemia [21].

Recent investigations focussed their interest on the implication of DDR-1 in renal disease. In an Ang II-induced hypertensive model of renal disease, it was shown that DDR-1 was overexpressed in renal vessels and glomeruli of treated mice. While systolic blood pressure increased similarly in Ang II-treated WT and DDR-1 KO mice, renal function and histology were significantly preserved in the second group. DDR-1 KO mice also showed a significant reduction in T lymphocyte and macrophage infiltration and in collagen I and IV deposition in renal tissue [22]. In a model of tubulointerstitial fibrosis (unilateral ureteral obstruction or UUO), DDR-1 was overexpressed in interstitial cells, especially macrophages [23]. Conversely, DDR-1 KO mice showed less perivascular inflammation and interstitial fibrosis. In *ex vivo* experiments, inflammatory cells isolated from DDR-1 KO mice showed reduced migratory activity [23]. Subsequent studies, investigated the role of DDR-1 in crescentic glomerulonephritis induced by antibodies against the glomerular basement membrane. Similar to the previous models, DDR-1 KO mice were protected in terms of renal function, histological lesions and mortality [24]. Similar results were obtained after the administration of specific

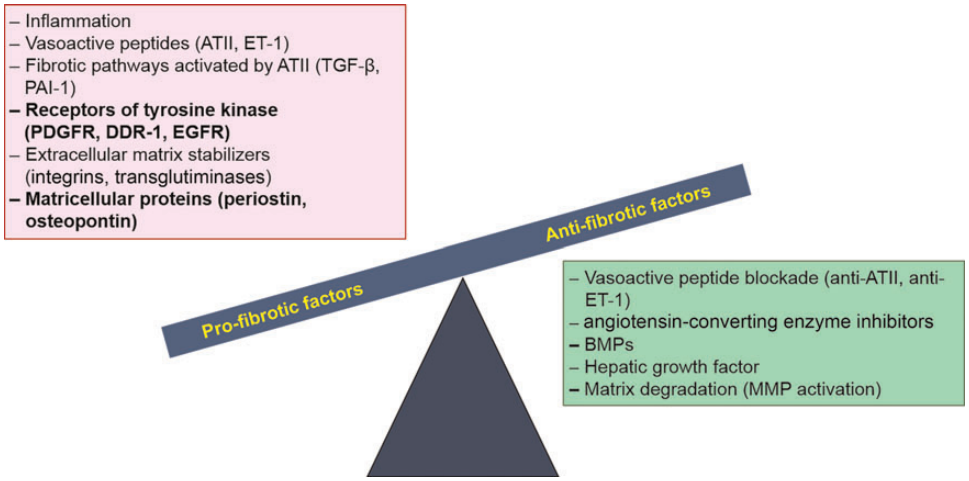

FIGURE 1: Progression or regression of fibrotic lesions depends on the balance between pro- and anti-fibrotic systems.

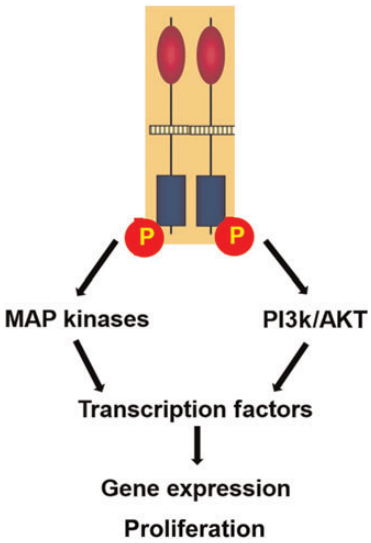

FIGURE 2: DDR-1 promotes the activation of transcription factors and gene expression through MAP Kinase and PI3 pathways.

antisense oligonucleotides for DDR-1. Clinical data regarding DDR-1 implication in human nephropathies and the potential role of its modulation in a therapeutic sense are still missing.

Inhibitors of tyrosine kinase receptors with a preferential selectivity for DDR-1 are under development, and experimental and clinical data have underscored their efficiency in treating cancers and haematological disorders. Until now, two of them have been tested and showed some promising effects: imatinib and nilotinib.

Imatinib is a non-selective inhibitor of several RTKs, including DDR-1. In particular, it is able to modulate the expression of PDGFR α and β, C-KIT and colony-stimulating factor-1 receptor [25]. All three of them are modulators of inflammatory and fibrotic processes [26]. Imatinib is nowadays used in patients with haematologic disorders such as chronic and acute myeloid leukaemia and gastrointestinal stromal tumours. It has been tested in many experimental studies with very encouraging results in diabetic, cryoglobulinaemic and lupus nephropathy models. Unfortunately, it is not free from side effects (occasional nausea, diarrhoea, periorbital oedema and muscle cramps), correlated with its non-selective inhibition of RTKs which results in epithelial toxicity. These limitations underline the need for specific therapeutic targets in order for selective inhibitors to be designed.

Nilotinib is a second-generation inhibitor of RTKs. It was tested in a model of chronic nephropathy with promising results. Unfortunately, its tolerance in humans remains to be demonstrated. Taking into account the capacity of both imatinib and nilotinib to modulate the immune response and inhibit fibrogenesis, a possible therapeutic role for them in diseases such as lupus erythematosus, chronic humoral rejection in kidney transplantation and cryoglobulinaemia has been hypothesized [27]. However, this is an emerging field of pharmacology and the recent description of novel selective and orally bioavailable DDR1 inhibitors will provide additional new tools to test the efficiency of blocking DDR1 in renal and other inflammatory/fibrotic diseases [28].

MPs AND PERIOSTIN: RECENT MEDIATORS IN RENAL FIBROSIS

Research about MPs and specifically periostin in renal diseases represents a promising recent field. ECM deposition is an important step in the progression of kidney injury. MPs are part of a class of ECM-related molecules that are able to bind to cell surface receptors (integrins) and to extracellular growth factors and collagens and modulate cell-matrix interactions [29]. Besides their normal expression during development, they are re-expressed in pathologies like fibrosis and cancer. Their role has mainly been studied in cancer, where a direct link between MP up-regulation, tumour growth and metastasis was demonstrated. In this context, MPs, produced by both tumour and surrounding stromal cells (fibroblasts and macrophages), modulate cellular adhesion and migration, ECM deposition and angiogenesis due to the regulation of TGF-β and other growth factors and their receptors, and to the stimulation of integrins that transduce pro-survival or pro-migratory signals. Most of these actions also induce a chronic low inflammatory

state, involved in tissue neoplastic transformation and tumour progression [30].

MPs have been recently reported in the pathogenesis of chronic glomerulopathies and tubulointerstitial diseases. In human crescentic glomerulonephritis, osteopontin is overexpressed in macrophages. Similarly, in a diabetic mouse model, a contribution of the MP SPARC in glomerulosclerosis and tubulointerstitial damage was detected and related to increased TGF-β1 expression [31]. Finally, thrombospondin was shown to regulate pathophysiological changes in different models of renal disease via activation of TGF-β, pro-apoptotic and pro-inflammatory mediators [32].

Periostin is an MP of 90 kDa originally named osteoblast-specific factor 2; its strong expression within the periosteum and periodontal ligament changed its name to that in use. The protein is composed of an N-terminal EMI domain rich in cysteine residues, which is the protein–protein interactions site [33]; a fasciclin I domain, containing four tandem Fas I domains, each composed of ∼150 amino acids; and the carboxyl-terminal domain, which includes a heparin-binding site at its C-terminal end. This site is frequently cleaved by proteolysis giving the protein-specific characteristics and functions (Figure 3).

For example, a specific cleavage at a region near the C-terminus of periostin (a heparin-binding site) was reported as essential for the association of periostin with tenascin-C. Normally, many pathways influence the expression of periostin. In bone diseases, it is up-regulated by c-fos, TGF-β, BMP-2, retinoic acid, PDGF, FGF-1 and FGF-2, and parathormone [34]. After its stimulation, periostin directly interacts via its EMI domain with collagen I, fibronectin and Notch-1 via its Fas I domain with tenascin C and BMP-1.

The generation of mice lacking periostin expression contributed to a better understanding of its biological role. Anomalies are detectable at 3 months in teeth and periodontal apparatus, with distinct radiographic signs of alveolar bone destruction and external root reabsorption and defective periodontal ligaments, reflecting a significant increase in osteoclast activity [35]. Subsequent studies demonstrated that these somatotropic defects are either due to malnutrition or to genetic background since some stabilized strains do not exhibit a particular phenotype. The importance of periostin in bone metabolism is also underscored by its re-expression after mechanical stress and fracture, participating in the repair processes due to its capacity of binding to cell-surface receptors modulating cell adhesion, proliferation, differentiation and cell-matrix interactions. Periostin overexpression has been described in the stroma of many tumours such as bone, non-small cell lung cancer, renal cell carcinoma and malignant pleural mesothelioma, and is associated with metastasis and poor prognosis.

The role of periostin in the heart and the lung under physiopathological conditions has also been investigated. Many of the observations in animal models seem to be reflected in humans. Periostin is highly expressed during embryogenesis and involved in valve and ventricular development [36]. After ischaemic injury and in advanced heart failure, periostin is abundantly expressed by cardiac fibroblasts in the infarct border in response to TGF-β1, reflecting the well-known direct link between TGF-β1 and periostin [37]. In this context, periostin seems to promote fibroblast migration through interaction with integrin αvβ3, production of collagen I and fibrillogenesis [38]. In patients with atherosclerotic and rheumatic valve disease, periostin expression is markedly elevated in the sub-endothelial layer of the valve, whereas its expression is reduced in the valves of infants with congenital bicuspid aortic valve stenosis [38].

With regard to lung diseases, in patients affected by idiopathic pulmonary fibrosis, it was demonstrated that periostin is produced by structural and inflammatory cells and is up-regulated during fibrotic responses. Moreover, serum periostin gives important information about the progression of the disease [39]. In asthmatic patients, the protein is secreted by activated airway epithelium into the underlying matrix where it has autocrine effects on epithelial cell function and paracrine effects on fibroblasts, probably contributing to airway remodelling [40]. In a recently published study in asthmatic patients, serum periostin levels were inversely correlated to the therapeutic response to lebrikizumab, a monoclonal antibody with anti-IL-13 function [41]. Involvement of periostin in many human cancers such as that of the lung, colon, pancreatic and breast has also been described. After binding to integrins, periostin activates signalling pathways that induce an increase of cell survival, angiogenesis and metastasis.

Periostin is expressed in the kidney during development and tissue remodelling, and has a role in tubulogenesis and

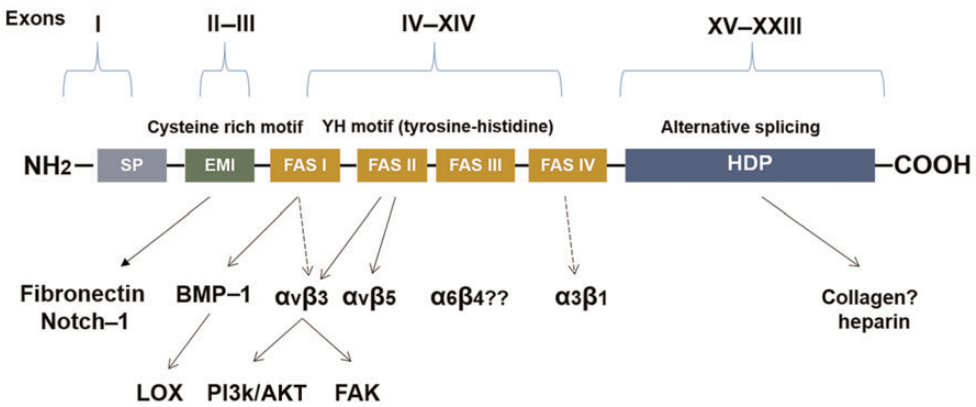

FIGURE 3: Structure and interactions of periostin.

vasculogenesis [42]. As in other organs, periostin is re-expressed during renal injury. The role of periostin in renal diseases has been studied in several models of kidney injury. In hypertensive nephropathy, its expression was correlated with the increase of blood pressure, and its levels were lower in the group of mice treated with RAS blockers [43]. Recently, it was shown that periostin, in addition to being a marker, can also mediate renal disease, and targeting its reactivation preserved the decline of renal function and structure. Thus, mice lacking the periostin gene showed less injury-induced interstitial fibrosis and inflammation in the UUO model [44]. In addition, *in vivo* delivery of antisense oligonucleotides to inhibit periostin expression protected animals from hypertension-induced renal injury. The mechanism of periostin action probably involves an interaction with the TGF-β pathway since *in vitro* administration of TGF-β to renal epithelial cells increased the expression of periostin several-fold, leading to subsequent loss of the epithelial phenotype [44].

In patients affected by autosomal dominant polycystic kidney disease, the periostin gene was one of the most abundant genes in cyst epithelial cells compared with normal tubular cells. Periostin expressed in renal cysts accelerates their growth and contributes to structural changes in the kidney, including interstitial fibrosis via αv-integrin signalling [45].

Periostin expression was also observed in biopsies from glomerular diseases [46]. Specifically, biopsies from patients with glomerulopathies and renal dysfunction were analysed and they revealed enhanced periostin expression in the mesangium, tubular interstitium and sites of fibrosis. Moreover, the increase of periostin staining correlated with the decline of the glomerular filtration rate in these patients. Periostin urinary excretion rates have been measured in a limited number of proteinuric and non-proteinuric CKD patients [47]. In a recent study performed with a small number of biopsies of transplanted kidneys, periostin was detected in glomerular, interstitial and vascular areas of injury. Moreover, in these patients, urinary

Table 1. DDR-1 and periostin involvement in human diseases

Authors	Year	Field of interest	Conclusions
DDR-1			
Ferri *et al.* [13]	2004	Atherosclerosis	In atherosclerotic lesions, DDR-1 is expressed in smooth muscle cells. Its phosphorylation leads to decreased collagen biosynthesis and increased collagen and elastin breakdown that modulate ECM remodelling.
Weiner *et al.* [14]	2000	Brain cancer	DDR-1 is expressed in high-grade brain neoplasms. It could be a potential marker of the tumour presence within the central nervous system.
Heinzelmann-Schwarz *et al.* [15]	2004	Ovarian cancer	DDR-1 up-regulation is an early event in the development of ovarian cancers and could aid in the early detection of disease.
Gu *et al.* [16]	2011	Liver cancer	Detection of activation of several ROS tyrosine kinases, DDR-1 included, in cholangiocarcinoma.
Ford *et al.* [20]	2007	Lung cancer	Association of DDR-1 with human lung cancer. DDR-1 is significantly up-regulated in patients and has a strong prognostic role.
Chiaretti *et al.* [21]	2005	Haematological disorders	High expression of DDR-1 in BCR/ABL-positive adult acute lymphocytic leukaemia.
Wallace and Gewin [27]	2013	Renal diseases	Possible beneficial effect of RTK inhibitors in human nephropathies: membranous nephropathy, systemic lupus erythematosus, chronic humoral rejection after renal transplantation and cryoglobulinaemic vasculitis.
Periostin			
Naik *et al.* [39]	2012	Idiopathic pulmonary fibrosis	In idiopathic pulmonary fibrosis, periostin is produced by structural and inflammatory cells and is up-regulated during fibrotic responses. Plasma periostin may be a useful biomarker to predict early progression of disease.
Sidhu *et al.* [40]	2010	Asthma	Periostin is secreted by airway epithelial cells and has both autocrine (activation of TGF-β, up-regulation of collagen-I) and paracrine effects (collagen production in fibroblasts). Its persistent up-regulation in the airway epithelium in asthma could increase airway fibrosis and decrease airway dispensability.
Corren *et al.* [41]	2011	Asthma	Patients with high levels of serum periostin respond better to treatment with brikizumab than patients with low serum periostin levels.
Wallace *et al.* [45]	2008	Autosomal dominant polycystic kidney disease	Increased expression of periostin accelerates cyst growth and modulates structural changes in the kidney (interstitial fibrosis). Periostin is overexpressed in human ADPKD cyst-lining cells and accumulates within the interstitium and cyst fluid of ADPKD kidneys *in situ*.
Sen *et al.* [46]	2011	Renal diseases	Periostin is increased in glomeruli of proteinuric patients. *De novo* expression, proportional to loss of renal function, is found also in the tubules and interstitium of CKD patients.
Satirapoj *et al.* [47]	2012	Renal diseases	Periostin is a marker of tubular de-differentiation and a promising tissue and urine biomarker for kidney injury in human renal disease.
Satirapoj *et al.* [48]	2014	Renal transplantation	Periostin could be used as a potential urine biomarker for chronic progressive renal injury in transplant recipients.
Braun *et al.* [49]	2013	Peritoneal dialysis	Periostin is expressed by fibroblasts and deposited in the peritoneal cavity of patients with encapsulating peritoneal sclerosis and with simple peritoneal fibrosis on peritoneal dialysis. It could modulate the progression of peritoneal injury.
Wantanasiri *et al.* [50]	2015	Lupus nephritis	Periglomerular overexpression of periostin, which is also present in fibrotic foci. The periostin staining score correlated with the chronicity index score and renal function in patients with lupus nephritis.

periostin showed a direct correlation with urine protein/creatinine ratio and serum creatinine [48].

In another recent retrospective study performed in patients undergoing peritoneal dialysis, a role for periostin in the development and progression of peritoneal fibrosis was hypothesized. In control peritoneal biopsies, the protein was constitutively present in the walls of larger arteries and focally in the ECM in the sub-mesothelial zone. In patients with encapsulating peritoneal sclerosis, its expression was mostly in the sclerotic layer. In a subgroup of patients periostin concentration in dialysate liquid was also evaluated and significantly increased with time in peritoneal dialysis in patients without signs of encapsulating peritoneal sclerosis [49]. Finally, the periostin staining score correlated with the chronicity index score of renal pathology and the worsening of renal function in patients suffering from lupus nephritis [50]. All these findings indicate a role for periostin not only as a mediator of but also as a prognostic factor for disease.

CONCLUSIONS

Drugs available nowadays are not sufficient to reduce the increase of prevalence and incidence of CKD worldwide. The recent identification of DDR-1 and periostin as potential mediators of injury in several organs and in different diseases subsequently led to the study of their roles in renal injury. Existing evidence so far, mainly derived from experimental models and supported by emerging data in patient cohorts (summarized in Table 1), shows that they have an important role in the onset and progression of renal injury, independent from the primary cause of disease. Periostin expression has been demonstrated in human renal disorders and may be used in the future to obtain diagnostic and prognostic information. DDR-1 still remains to be characterized in these disorders. However, new perspectives in this field must consider the effect of DDR-1 and periostin modulation with the aim to develop drugs capable of reducing the progression of renal injury.

CONFLICT OF INTEREST STATEMENT

None declared.

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