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Review

Renal fibrosis in feline chronic kidney disease: Known mediators and mechanisms of injury

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ABSTRACT

Chronic kidney disease (CKD) is a common medical condition of ageing cats. In most cases the underlying aetiology is unknown, but the most frequently reported pathological diagnosis is renal tubulointerstitial fibrosis. Renal fibrosis, characterised by extensive accumulation of extra-cellular matrix within the interstitium, is thought to be the final common pathway for all kidney diseases and is the pathological lesion best correlated with function in both humans and cats. As a convergent pathway, renal fibrosis provides an ideal target for the treatment of CKD and knowledge of the underlying fibrotic process is essential for the future development of novel therapies. There are many mediators and mechanisms of renal fibrosis reported in the literature, of which only a few have been investigated in the cat. This article reviews the process of renal fibrosis and discusses the most commonly cited mediators and mechanisms of progressive renal injury, with particular focus on the potential significance to feline CKD.

Introduction

Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities of one or both kidneys that have been present for an extended period of time. CKD is common in cats, one study reporting that 12% of all cats necropsied over a period of 3 years were suffering from the condition (Taugner et al., 1996). The prevalence of CKD also increases with age, with reported prevalence rates of 28% in cats over 12 years old (Bartlett et al., 2010) and 31% in cats over 15 years old (Lulich et al., 1992).

The aetiology of feline CKD is heterogeneous and includes specific disease processes which initiate renal damage or dysfunction, such as polycystic kidney disease, renal amyloidosis, renal dysplasia and renal lymphoma (Reynolds and Lefebvre, 2013). However in the majority of cats with CKD no inciting cause is identified. One study of a referral population found pathological lesions of a specific renal disease in 50% of cases (DiBartola et al., 1987), another in 33% of cases (Minkus et al., 1994). A recent study with a large population from first opinion practices identified specific renal lesions in only 16% of cats (Chakrabarti et al., 2013). The majority of cats with CKD are found to have non-specific renal lesions and the predominant morphological diagnosis in these cases is chronic tubulointerstitial inflammation and fibrosis (DiBartola et al., 1987; Chakrabarti et al., 2013).

The underlying aetiology of CKD in the majority of cats, where chronic tubulointerstitial fibrosis is present, is not understood. Various factors which may contribute to renal damage have been proposed, including diet (Hughes et al., 2002), vaccination (Lappin et al., 2006), and ageing (Lawler et al., 2006). Regardless of the aetiology, the progressive nature of renal fibrosis results in deterioration of renal function independent of the initial renal insult. Renal tubulointerstitial fibrosis is recognised as the final common pathway for all kidney diseases in human patients regardless of aetiology (Prunotto et al., 2011) and is the pathological lesion best correlated with renal function in both humans (Risdon et al., 1968; Nath, 1992) and cats (Yabuki et al., 2010; Chakrabarti et al., 2013).

Despite ongoing research there is currently no effective treatment that significantly slows the progression of renal fibrosis in humans or in cats. Therefore, much attention is directed at identifying factors which influence or drive the progression of fibrosis in order to identify potential therapeutic targets. The aim of this article is to provide a review of the renal fibrotic process and evaluate previous research published on mediators and mechanisms of renal fibrosis, with particular focus on those investigated in cats, in order to provide updated information for veterinary clinicians and pathologists.

Renal fibrosis

In most cases of tissue damage, injured cells are replaced by cells of the same type and/or fibrous tissue after the resolution of the inflammatory response. The kidney has an intrinsic capacity for

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self-repair after ischaemic or toxic insults that result in cell death and can potentially recover completely after sustaining acute injury. This repair occurs primarily through epithelial cell proliferation, and it appears that an intact basement membrane plays an important role by providing a scaffold along which regenerating epithelial cells can spread and migrate (Toback, 1992; Bonventre, 2003). Healing via focal fibrotic scarring is also seen secondary to severe parenchymal injury, for instance in pyelonephritis or infarction, and serves to maintain tissue integrity. Whilst fibrosis is a normal sequel of injury, it is thought that in CKD the normal wound healing response fails to terminate (Liu, 2006; Wynn, 2010). Although the exact mechanisms underlying this dysregulation are unclear, the result is an excessive, inexorable fibrogenic response and the expansion of the extra-cellular matrix (ECM) gradually destroys normal tissue structure (Eddy, 1996). The histopathology of renal fibrosis features excessive accumulation of ECM proteins within the tubulointerstitial space and is accompanied by loss of the renal microvasculature, infiltration of mononuclear cells, tubular atrophy and dilation (Fig. 1). The aberrant extracellular matrix is composed of normal matrix proteins and proteoglycans as well as other matrix proteins normally restricted to tubular basement membranes, such as collagen IV and laminin (Vleming et al., 1995; Eddy, 1996).

In the normal kidney, interstitial fibroblasts play a crucial role in ECM homeostasis via their dual roles in the synthesis of ECM and production of ECM degrading proteases (Strutz and Zeisberg, 2006). In fibrogenesis, these cells are believed to become activated and undergo a phenotypic change to become myofibroblasts. The induction and proliferation of myofibroblasts is probably a crucial event in the initiation and progression of renal fibrosis. Myofibroblasts possess qualities of both fibroblasts and smooth muscle cells and are considered the dominant ECM producing cells in organ fibrosis (Prunotto et al., 2011; Lebleu et al., 2013). It is not possible to differentiate these cells from fibroblasts via light microscopy and they are characterised by their expression of alpha smooth muscle actin (α-SMA) and vimentin. Both vimentin and α-SMA expression increase within the kidney in naturally occurring feline CKD and the expression of these cellular markers correlates with increasing plasma creatinine concentration and kidney fibronectin deposition (Sawashima et al., 2000; Yabuki et al., 2010).

The precise origin of myofibroblasts has historically been controversial, and several cell types as well as resident fibroblasts are known to undergo phenotypic changes to ECM producing cells in renal fibrosis, including tubular epithelial cells, circulating fibrocytes, vascular pericytes, endothelial cells and glomerular podocytes (Kim et al., 2013). The relative contribution of these cellular types to the myofibroblast pool is the focus of ongoing investigation. One recent comprehensive analysis examining the relative contribution of various cell types to the myofibroblast lineage, using mice with experimentally induced obstructive renal disease, found that 50% of the population arose from proliferation of resident fibroblasts whilst the remainder differentiated from bone marrow derived cells (35%), endothelial cells (10%) and epithelial cells (5%) (Lebleu et al., 2013).

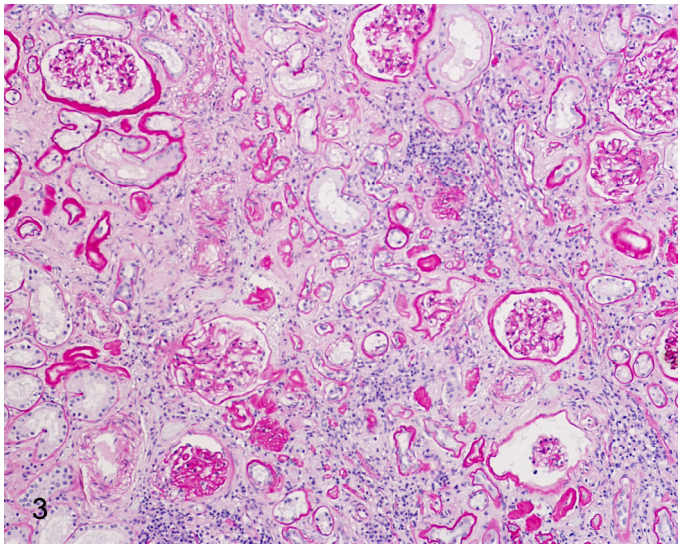

Fig. 1. Photomicrograph illustrating severe cortical interstitial fibrosis and inflammation in the kidney of a cat with CKD. Periodic acid-Schiff and haematoxylin. Reprinted with permission from *Veterinary Pathology*, SAGE publications.

Myofibroblast induction, proliferation and ECM production are regulated by a number of local and circulating factors. These include paracrine or autocrine growth factors, direct interaction with leucocytes/macrophages, and environmental stimuli such as hypoxia and hyperglycaemia (Qi et al., 2006). Recent studies have also emphasised the importance of renal tubular epithelial cell damage and altered epithelial–mesenchymal cell signalling in the activation of renal fibroblasts towards the myofibroblast type in CKD (Prunotto et al., 2012; Moll et al., 2013).

Pro-fibrotic mediators

Transforming growth factor beta (TGF-β)

The cytokine TGF-β is potentially the most important profibrotic mediator responsible for myofibroblast activation, appearing to be a convergent pathway that integrates the effects of many other fibrogenic factors (Liu, 2006; Farris and Colvin, 2012). TGF-β1 is the most abundant isoform and is synthesised by all cell types of the kidney, with epithelial cells demonstrated to be the main source in experimentally induced disease (Fukuda et al., 2001; Wu et al., 2013). TGF-β is secreted as a latent precursor and must undergo proteolytic cleavage in order for the active form of the cytokine to be liberated, which may be initiated directly by a variety of molecules including plasmin and reactive oxygen species (Annes et al., 2003). Once activated, TGF-β exerts its subsequent effects by binding to the TGF-β receptor II and regulating the transcription of target genes (Wang et al., 2005). Production of TGF-β has been demonstrated to be induced by a variety of stimuli, including the renin–angiotensin–aldosterone system (Wolf, 2006), hypoxia (Orphanides et al., 1997), proteinuria (Eddy and Giachelli, 1995), increased single nephron glomerular filtration rate (Rohatgi and Flores, 2010) and oxidative stress (Shin et al., 2008).

TGF-β is upregulated in nearly all mammalian chronic kidney diseases, and evidence from rodent models supports the hypothesis that TGF-β signalling is central to the induction of kidney disease. Mice overexpressing TGF-β develop interstitial fibrosis (Koesters et al., 2010) and downstream disruption of the TGF-β signalling pathway has been demonstrated to ameliorate renal fibrosis (Sato et al., 2003). The profibrotic effects of TGF-β include inducing the formation of myofibroblasts from various cell types in vitro, including fibroblasts (Serini et al., 1998), pericytes (Wu et al., 2013) and potentially also endothelial cells (He et al., 2013), although the relative significance of these findings in vivo is controversial. It directly stimulates transcription of ECM genes in many renal cells, including tubular, endothelial and mesangial cells (Border and Noble, 1993) and also decreases matrix degradation (Edwards et al., 1987; Krag et al., 2005). TGF-β1 signalling in tubular epithelial cells alone, independent of myofibroblasts, is sufficient to cause tubular injury, apoptosis and accumulation of inflammatory cells (Gentle et al., 2013). As well as direct effects, TGF-β also acts to stimulate cell proliferation and ECM accumulation through downstream activation of the pro-fibrotic cytokine connective tissue growth factor (CTGF) (Grotendorst, 1997).

TFG-β (normalised to urinary creatinine) has been shown to be present in increased concentrations in the urine of cats with