Experimental Strategies to Reverse Chronic Renal Disease

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Key Words

Chronic renal injury reversal · Renal replacement therapy · Renin-angiotensin system · Transforming growth factor- β_1 · Bone morphogenic protein-7 · Hepatocyte growth factor

Abstract

Progression of chronic nephropathies still represents a major challenge for clinical nephrologists. Specific therapies that prevent patients from requiring dialysis or transplantation are still not available. However, recent experimental studies have demonstrated that regression of advanced lesions in the kidney can be achieved. This review summarizes the recent therapeutic advances using experimental models that might translate into novel human therapies to prevent, or significantly delay, requirement of renal replacement therapy.

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Dialysis therapy and organ transplantation are sufficient to circumvent the instant fatality due to end-stage renal failure [1]. However, both options still offer problems, such as high costs, limited availability, reduced quality of life and overall prognosis. Adequate pharmacotherapy to inhibit the progression of chronic kidney dis-

ease (CKD) is still one of the biggest challenges of clinical nephrologists [1, 2]. While slowing the rate of progression of chronic renal disease has been the principal goal in recent decades, recent animal studies have suggested that improvement of renal function and associated structural injury is potentially achievable.

The rationale for such thinking is the following: First, the kidney possesses an enormous capacity to regenerate following acute injury [3]. Utilization of this endogenous regenerative capacity of the kidney in chronic disease setting could lead to repair of the injured kidney. Second, many forms of CKD evolve to end-stage renal failure through a series of common events that are relatively independent of the underlying insult [2, 4]. Blocking of these common events could then inhibit, or even reverse, chronic renal injury, independent of the underlying primary disease.

CKD is characterized by the triad of glomerulosclerosis, interstitial fibrosis and tubular atrophy [4]. Tubulointerstitial fibrosis, which is defined by excessive deposition of extracellular matrix in association with tubular atrophy, is currently the morphologic predictor, which is most tightly linked to chronic progressive injury [2, 4]. The main cellular events that mediate progression of tubulointerstitial fibrosis are activation (enhanced proliferation and extracellular matrix deposition) of resident fibroblasts and epithelial-mesenchymal transition (EMT, tu-

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Fig. 1. A The schematic displays the major cellular populations of the nephron in a normal kidney: Podocytes (green), glomerular endothelial cells (EndCs, orange), mesangial cells (MesCs, purple) in the glomerular compartment and fibroblasts (purple) and tubular epithelial cells (TECs, blue) in the tubulointerstitial compartment. **B** The schematic displays the main pathologic that contribute to kidney fibrosis and the cellular targets of ACE inhibitors (ACE-Is), HGF and BMP-7. Main features of glomerulosclerosis are mesangial expansion and podocyte injury, principal mediators of tubulointerstitial fibrosis are EMT (leading to tubular atrophy and increased fibroblast population) and fibroblast activation. ACE-Is can directly ameliorate glomerular injury (red line). HGF has been shown to ameliorate glomerulosclerosis (red line) and to inhibit fibroblast activation and EMT (black lines). BMP-7 could reverse glomerular hypertrophy, fibroblast activation and EMT in animal models of kidney injury.

bular epithelial cells becoming fibroblasts) [5, 6]. Thus, requirements to achieve reversal of chronic renal injury are the inhibition of fibroblast activation, prevention or even reversal of EMT and enhanced matrix degradation, which should exceed the interstitial matrix deposition (fig. 1).

A paradigm for the inevitable progression to end-stage renal failure due to chronic renal disease was questioned for the first time in a 10-year follow-up study of patients with diabetic nephropathy who received pancreatic islet transplantation [7, 8]. In this study, a significant number of patients with established glomerular and interstitial disease, exhibited reversal of kidney function and marked histological improvement 10 years after pancreatic islet transplantation [7]. This report strongly suggested that established fibrosis in kidneys could regress, if the primary pathogenic stimulus is removed or significantly dialed down [7, 9]. Capacity to re-build and repair chronically diseased kidneys suggested the presence of endogenous molecules, which could mediate this physiologic repair process [7, 9]. The mechanism, through which regression of chronic renal injury was achieved, remained unclear in that report. However, in a series of animal studies, which attempted to study the biology of regression of chronic renal injury, some insights were gained (see below).

Renin-Angiotensin System

Inhibition of the renin-angiotensin system (RAS) by ACE inhibitors or angiotensin receptor blockers (ARBs) is the current gold standard in the clinic to retard the progression of chronic renal disease (reviewed by Brenner [10]). A potential for clinical utility of ACE inhibitors to inhibit progression of chronic renal failure, independent of its antihypertensive effect, was first demonstrated by Anderson et al. [11] in a rat model for chronic renal failure. ACE inhibitors and ARBs were first shown to inhibit the progression of diabetic nephropathy and also to inhibit progression of non-diabetic chronic renal disease [10]. Several animal studies have now demonstrated that ACE inhibitors can also revert early glomerulosclerotic lesions [10, 12, 13]. In Munich-Wistar-Frömter rats with spontaneous renal disease, ACE inhibitors which were given late during the disease (when animals have already developed heavy proteinuria), decreased proteinuria and lowered the incidence sclerotic glomerular lesions as compared to untreated controls [14]. Recent animal studies using hypertensive rat models could further demonstrate regression of glomerular lesions [15, 16]. Although repair of advanced tubulointerstitial injury/fibrosis could not be achieved with ACE inhibitors and ARBs.

Transforming Growth Factor- β_1

Transforming growth factor- β_1 (TGF- β_1) has been identified as the main mediator leading to progression of CKD [17]. Numerous studies have confirmed, that some of the main cellular events leading to tubulointerstitial fibrosis (fibroblast activation, EMT and glomerulosclerosis), are mediated by TGF- β_1 . Therefore, different experimental studies have attempted to directly target TGF- β_1 [18, 19]. More than a decade ago now, Border et al. [20] reported that suppression TGF- β_1 by injection of neutralizing antibodies inhibited the progression of chronic renal disease in an animal model of acute mesangial proliferative glomerulonephritis. This report was followed by a series of studies which confirmed that targeting of TGF- β_1 by using several different TGF- β_1 traps such as the endogenous molecule decorin, neutralizing antibodies or soluble receptors could inhibit progression of renal chronic renal disease in a variety of animal models mimicking human disease [21–24]. All these studies however demonstrated inhibition and not reversal of already established lesion, except for one study, which targeted TGF- β_1 by administration of neutralizing antibodies, and reported improvement of renal pathology in a mouse model of cyclosporin A nephropathy [25].

While TGF- β_1 appears to be a promising target for treatment of chronic renal disease, several potential problems need to be addressed before long-term administration of TGF- β_1 -binding molecules is considered [26]. In addition to its role in fibrosis, antagonism of TGF- β_1 has proven to be beneficial in targeting tumor metastasis, parasite infections and immunosuppression [26–28]. In contrast, loss of TGF- β_1 function has also been implicated in the pathogenesis of cancer, atherosclerosis, autoimmunity and inflammatory diseases [26, 29]. Thus, ideally in the clinical setting one would like to selectively neutralize the TGF- β_1 when involved in disease pathogenesis without affecting the normal homeostatic roles of TGF- β_1 in unaffected tissues.

Bone Morphogenic Protein-7

Bone morphogenic proteins (BMPs) are a major subgroup of the TGF- β superfamily [30]. Traditionally, BMPs are classified into three groups [30]. The first group contains BMP-2 and BMP-4, the second contains BMP-5, BMP-6 and BMP-7, and the third contains BMP-3 and BMP-8 [30]. BMPs, in general, control morphogenic pathways at different stages of development [31]. BMP-7, also

sometimes referred to as osteogenic protein-1 (OP-1), was originally identified as a potent osteogenic factor purified from bone [32]. Different studies have demonstrated a role for BMP-7 during mammalian kidney development [33, 34]. Homozygous BMP-7-deficient mice have dysplastic kidneys and die shortly after birth from renal failure [33, 34]. In these mutants, formation of S-shaped tubules is initiated, but gets arrested at embryonic day 11.5 [33, 34]. In the adult kidney, BMP-7 is robustly expressed, mainly in the collecting duct, distal tubular epithelial cells and podocytes [35]. Acute and chronic renal injury is associated with a significant decrease of BMP-7 expression levels (sometimes up to 10-fold reduction) [36]. Since recovery of renal function after acute injury is associated with normalization of BMP-7 levels in the kidney, a putative reno-protective role of endogenous BMP-7 was postulated [36].

BMP-7 and Acute Renal Injury

Two independent groups investigated the renal expression of BMP-7 in a rat model of ischemic acute renal failure and reported similar results that upon injury BMP-7 expression in the kidney is reduced by about 10-fold. [37, 38]. These results are also validated now in several other acute and chronic renal disease models in our laboratory [unpubl. data; 39]. BMP-7 mRNA is detected in tubules of the outer medulla, glomeruli and collecting duct cells [37, 38]. Expression of BMP-7 is significantly decreased 6 h following the ischemic insult and expression levels were still significantly lower 4 days after injury [37, 38]. The decrease of BMP-7 expression is most significant in the outer medulla [37, 38]. Administration of rhBMP-7 protects the mice from ischemia-induced acute injury [37]. Tubular necrosis is reduced, pro-inflammatory adhesion molecules are decreased, apoptosis is reduced and functional recovery of the ischemic kidneys is accelerated. Interestingly, binding studies using ^{125}I -BMP-7 demonstrates an abundant binding in the kidney cortex [37]. Decrease of BMP-7 expression is reciprocal to TGF- β expression, suggesting an important role for BMP-7 in the maintenance of renal homeostasis in the acute injury setting [38]. These studies suggest that while TGF- β_1 is a biological marker for the progression of kidney disease (accepted for many years now), for the time BMP-7 is emerging as a possible biological marker for the improvement of renal function and histology. Therefore, let us examine its role in the chronic disease setting.

BMP-7 and Chronic Renal Injury

Subsequent to observations in the acute injury models which suggested a role for BMP-7 in maintenance of tubular homeostasis, human recombinant BMP-7 (rhBMP-7) was provided by Creative Biomolecule, Inc./Curis, Inc. to a number of groups to investigate its potential in inhibiting progression of acute and chronic renal disease, in their favorite in-house renal disease models. Evidence for BMP-7 as a potential antifibrotic agent was observed by several independent groups in different models of renal disease, including our group.

Hruska et al. [40] reported that administration of rhBMP-7 ameliorated tubular damage and interstitial injury observed in rats 5 days after unilateral ureteral obstruction. Treatment with BMP-7 was superior to treatment with enalapril (an ACE inhibitor) in this study [40]. In a subsequent study they also report that BMP-7 accelerates de novo recovery of renal function when the unilateral ureteral obstruction was removed after 3 days [41]. In contrast, the same research group did not observe amelioration of renal disease in a mouse model of renal mass ablation [42]. Our research group provided further evidence for BMP-7 as an antifibrotic agent in a genetic model of lupus nephritis [43]. Treatment of MRI/MpJ lpr/lpr mice with BMP-7 over a period of 4 months significantly prevented interstitial fibrosis and tubular atrophy in this long-term model of chronic renal injury [43]. During the same period, Ikeda et al. [44] demonstrated that treatment with BMP-7 was associated with less interstitial fibrosis in a rat model of overload proteinuria after 6 weeks. Interestingly, in this study, expression levels of TGF- β mRNA were increased despite a trend towards improvement of renal histology and excretory function [44]. In a different study, Nadim et al. [45] provided evidence that treatment with BMP-7 for 10 weeks reduced glomerulosclerosis and tubulointerstitial injury, independent of effects on the systemic blood pressure, in a rat model of 5/6 renal mass ablation.

Interestingly, Klahr et al. [36] reported that treatment with BMP-7 ameliorated glomerular pathology and tubulointerstitial fibrosis in a model of STZ-induced diabetes. In summary, several independent studies performed by different groups have unequivocally demonstrated that administration of BMP-7 could inhibit the progression of fibrosis in different animal models of CKD.

Mechanism of Action for BMP-7 in the Kidney

TGF- β_1 has long been identified as the major mediator of renal fibrosis and recent studies have provided increasing evidence that BMP-7 functions as a physiological antagonist of TGF- β_1 [19, 46]. BMP-7 is essential for MET-dependent nephrogenesis and branching morphogenesis, while TGF- β_1 induces apoptosis of the metanephric mesenchyme and inhibits branching of the ureteric bud [47]. In the adult kidney, increased expression of TGF- β_1 is associated with progression of chronic renal disease, while the expression of BMP-7 in the kidney is significantly decreased in injured kidneys [46, 48]. TGF- β_1 induces chemokine release, apoptosis and EMT involving tubular epithelial cells, all of which are believed to contribute to the progression of renal fibrosis. BMP-7 decreases the release of pro-inflammatory growth factors from tubular epithelial cells [35], treatment with BMP-7 reduces the apoptotic rate of tubular epithelial cells in a rat model of UUO [40], it reduces the secretion of ECM constituents by tubular epithelial cells [49] and it reverses EMT [46]. TGF- β_1 mediates pro-fibrotic effects on renal fibroblasts, as it induces synthesis of ECM constituents and fibroblast proliferation. BMP-7 inhibits secretion of interstitial ECM constituents, suggesting that it also counteracts TGF- β_1 action in interstitial fibroblasts [39].

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is another endogenous molecule, with a capacity to protect kidney from injury. HGF was originally characterized as a potent mitogen for liver cells [50]. During kidney development, HGF is associated with scattering of epithelial cells during tubulogenesis [51]. Administration of exogenous HGF has now been reported to ameliorate injury in several models of renal disease [52], whereas blockade of endogenous HGF by administration of a specific antibody markedly worsens kidney function with morphologic evidence for renal injury [53]. HGF is shown to have antifibrotic effects, blocks epithelial to fibroblast transdifferentiation and stimulates matrix degradative pathways [54]. A recent study demonstrated the potential of HGF to ameliorate established renal injury [55]. However, not all studies have demonstrated a beneficial effect of HGF on chronic renal injury. For example, in transgenic mice that overexpress HGF, progressive renal injury was observed, characterized by cyst formation, tubular hyperplasia, and glomerular sclerosis [56]. More relevant, Laping et al. [57]

reported that administration of HGF to a strain of diabetic mice was associated with a reduction in creatinine clearance and an increase in albumin excretion. An explanation for such divergent results in different models of chronic renal disease is not clear.

Conclusion

Recent animal studies have suggested that the kidney possesses signaling pathways, which can be engaged to mediate the repair of chronically injured kidneys. In animal models for renal injury, three different approaches (administration of BMP-7 or HGF and inhibition of the RAS) have been suggested to stimulate repair of kidney tissue (fig. 1). These studies suggest that most promising targets in the kidney to reverse chronic renal injury involve EMT associated with tubular epithelial cells/

fibroblast activation (fig. 1). These studies further suggest that severely damaged kidneys in a chronic setting still possess the capacity to repair, though to a lesser extent when compared to kidneys with acute injury. Such regenerative capacity of the kidney might be a relict from pathways associated with developmental steps and such endogenous programs can be potentially manipulated to facilitate repair of the kidney. Research must proceed at full speed to determine whether such pathways and programs can be harnessed to repair injured kidney associated with CKD.

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