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EDITORIAL COMMENTARY

Reversal of experimental renal fibrosis by BMP7 provides insights into novel therapeutic strategies for chronic kidney disease

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Abstract Bone morphogenic protein-7 (BMP7) is a morphogen that is important for kidney development and which is also an integral part of the kidney's physiological response to repair of acute kidney injury. Several studies demonstrate that preexisting renal BMP7 pathways can be utilized by administering recombinant BMP7 to protect the kidney in experimental models of chronic kidney disease (CKD). Effectiveness of recombinant BMP7 in animal studies raises the possibility that the BMP7 pathway could be equally utilized to treat patients with CKD and interstitial fibrosis. However, regulation of BMP7 activity in the kidney is complex. BMP7 activity in the kidney is not only determined by availability of BMP7 itself, but also by a balance of agonists, such as Kielin/chordin-like protein (KCP) or BMP receptors, and antagonists including gremlin, noggin, or uterine sensitization-associated gene-1 (USAG-1). Presence of BMP7 agonists and antagonists has to be considered when recombinant BMP7 is supplemented to treat injured kidneys. Here we summarize recent insights into the role of BMP7 in acute and chronic kidney injury and discuss the implications for future directions of antifibrotic therapies.

Keywords Bone morphogenic protein (BMP) · Chronic kidney disease (CKD) · Fibroblasts · Epithelial–mesenchymal transition (EMT) · Fibrogenesis · Scarring

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Introduction

Over the past decade various studies have demonstrated the efficacy of bone morphogenic protein-7 (BMP7) to inhibit or reverse fibrosis in experimental models of chronic kidney disease (CKD) [1]. Murine models responsive to BMP7-therapy include the mouse model of unilateral ureteral obstruction (a model for obstructive nephropathy) [2], nephrotoxic serum nephritis (a model for acute glomerulonephritis) [3], renal fibrosis associated with streptozotocin-induced diabetes mellitus (a model for diabetic nephropathy) [4], $MRL^{lpr/lpr}$ mutant mice (which develop lupus-like glomerulonephritis), and *collagen IV* $\alpha 3$-deficient mice (a mouse model for Alport syndrome) [5]. Recombinant BMP7 inhibits progression of fibrosis in a variety of mouse models of renal fibrogenesis. This raises interest as to whether targeting the BMP7 pathway could be beneficial for patients with CKD (Fig. 1).

BMP7 structure and function

BMP7 is a morphogen that is abundantly present in kidney, bone, and cartilage [1]. BMP7 is one of 15 known BMPs that are structurally and functionally related and are part of the transforming growth factor beta (TGF-β) superfamily of growth factors [6]. BMPs in general are best known for their role as morphogens during embryonic development, but they also regulate growth, differentiation, chemotaxis,

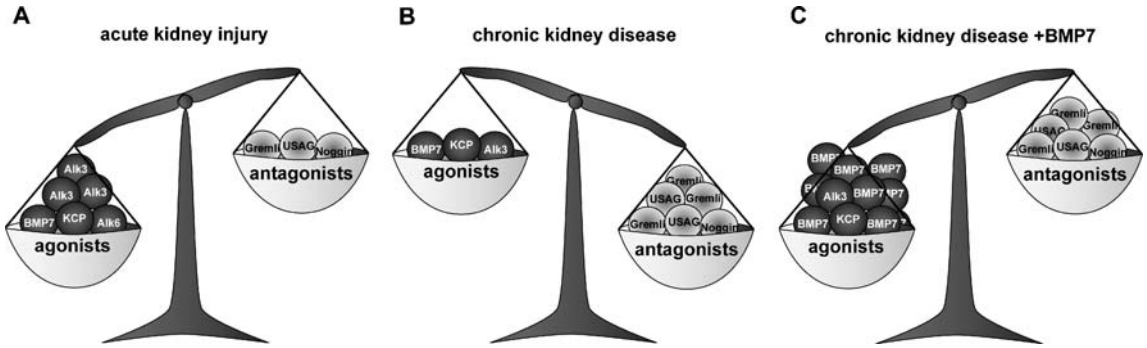

Fig. 1 BMP7 activity in the diseased kidney is determined by the presence of BMP7 and its receptors ALK3 and ALK6. Additionally, the balance of extracellular antagonists— which bind to BMP7 and prevent it from binding to its receptor and agonists that enhance receptor binding—modulates BMP7 activity. Such antagonists include noggin, gremlin and USAG-1. KCP enhances BMP7 activity. **A** In experimental acute kidney injury that resolves spontaneously, BMP7 activity is high. **B** In chronic kidney disease, BMP7 expression is low and antagonists outweigh BMP7 agonists. BMP7 activity is low. **C** Administration of recombinant BMP7 can compensate for the loss of endogenous BMP7 expression, and the agonists outweigh BMP7 antagonists. Resulting BMP7 activity facilitates repair of chronic renal injury. *BMP7* bone morphogenic protein-7, *ALK3* activin-like kinase-3, *ALK6* activin-like kinase-6, *USAG-1* uterine sensitization-associated gene-1, *KCP* Kielin/chordin-like protein, *Gremli* gremlin

and apoptosis of various adult cell types, including epithelial, mesenchymal, hematopoietic, and neuronal cells [7]. BMP7 was originally identified as a bone morphogen (and initially named osteogenic protein-1) [8]. *BMP7* knockout mice die shortly after birth due to diffuse renal dysplasia, revealing that BMP7 is indispensable for normal kidney development. BMP7 is synthesized as a large precursor protein that contains a signal sequence and a prodomain, and the mature, biologically active BMP7 is generated by proteolytic removal of the signal peptide and propeptide and glycosylation at various sites [9]. Due to the manifold modifications, BMP7 is a heterogenous mixture of differentially processed proteins [9]. As a result, generation of large amounts of recombinant BMP7 with homogenous activity has been notoriously difficult.

Molecular mechanisms underlying BMP7-mediated reversal of renal fibrosis

In the adult kidney, BMP7 is endogenously expressed in epithelial cells of distal tubules and collecting ducts [10]. Endogenous BMP7 expression is diminished in the experimental models of kidney injury. Furthermore, overexpression of BMP7 protects the kidney from injury, confirming the notion that the role of endogenous BMP7 in the kidney is to facilitate repair of renal injury [11]. In the diseased kidney, BMP7 affects cell types that are derived from the metanephric mesenchyme. Whereas tubular epithelial cells are the primary beneficiaries of BMP7, BMP7 also acts on podocytes [12], mesangial cells, and fibroblasts [13]. In addition, BMP7 may also protect the peritubular microvasculature from injury [14]. In all these cell types, BMP7 antagonizes TGFβ action, the ultimate profibrotic growth factor [3].

Evidence is evolving to show that the renoprotective activity of BMP7 is not exclusively determined by presence of BMP7 protein but also by a complex balance of agonists and antagonist. In the healthy kidney, BMP7-elicited activity is not apparent (even though BMP7 expression is high), whereas the injured kidney is responsive to BMP7, just as is the kidney during embryonic development [1, 15]. The molecular mechanisms that regulate such context dependency of BMP7 activity in the kidney are incompletely understood yet are highly relevant to potentially utilize the endogenous BMP7 pathway for clinical use.

The biological activity of BMP7 in the kidney is controlled at various levels. At the site of the target cells, signal transduction in the BMP7 in general is initiated by ligand binding to a receptor complex composed of two type I receptors and two type II receptors [1]. Three different BMP type I receptors (activin receptor-like kinase ALK2, ALK3, and ALK6) and three BMP type II receptors [(BMPRII), activin type IIA receptor (ACTRIIA), and activin type IIB receptor (ACTRIIB)] have been identified [1]. Renal injury is associated with increased expression of BMP type I receptors, suggesting that BMP7 activity in health and disease is also partially regulated by availability of its receptors [16]. BMP type II receptors are constitutively expressed and are not regulated in disease progression.

Several extracellular molecules have been identified that bind to BMP7, acting as agonists or antagonists in the kidney [7]. BMP antagonists function through direct association with BMPs, thus prohibiting BMPs from binding to their cognate receptors. Such extracellular inhibitors of BMP signaling include noggin, gremlin,

CRIM1, DAN/Cerebrus, vertebrate chordin, and uterine sensitization-associated gene-1 (USAG-1) [1]. In contrast, Kielin/chordin-like protein (KCP) protein is an extracellular protein that enhances BMP7 activity by increasing BMP7 binding to its receptor [15].

Overall, the relevance of altered presence of BMP7 agonists and antagonists or BMP7 itself on CKD progression is not entirely clear. As opposed to mouse models of CKD, BMP7 expression is often even increased in biopsies from patients with CKD [17]. However, expression of the BMP7 antagonist gremlin is markedly upregulated in areas of tubulointerstitial fibrosis associated with diabetic nephropathy, possibly accounting for the loss of endogenous BMP7 activity in the chronically diseased kidney [18]. In summary, there are multiple ways to turn off BMP7 signaling in the diseased kidney. This means that the underlying mechanism for decreased BMP7 activity may have to be determined on an individual basis.

Implications for experimental strategies to reverse chronic kidney disease

The effectiveness of BMP7 to inhibit or reverse fibrosis in mouse models of CKD revealed insights into how progressive renal fibrosis can be targeted. Our lessons from these experimental studies are summarized below.

1. Reversibility of CKD-associated fibrosis

Our studies demonstrated that treatment with rhBMP7 reverses established fibrotic lesions in the nephrotoxic serum nephritis (NTN) mouse model (a model for acute glomerulonephritis leading to severe tubulointerstitial fibrosis within 6–9 weeks in mice) [3]. Whereas the dynamics of fibrosis progression are different in humans and the underlying pathomechanisms far more complex, this raises the possibility that patients with CKD could be similarly responsive to antifibrotic therapy. Whereas antifibrotic therapies may not be available in the clinic as yet, this might be the time to change the perception that fibrosis is untreatable.

2. Reinduction of developmental programs to reverse chronic renal fibrosis

Tissue repair upon injury resembles embryogenesis in many ways, as both involve a coordinated series of cell proliferation, cell migration, and tissue contraction [19]. Such thinking led to the concept that factors mediating embryogenesis, such as BMP7, could be utilized to enhance tissue repair. This concept is even more intriguing, as embryos posses the capacity to fully regenerate upon tissue injury (embryonic skin wounds are the most extensively studied example) without scar formation [19]. Such regenerative capacity is increasingly lost after birth, and instead, tissues react to injury by forming a scar [19]. Because fibrosis is a pathological form of wound healing that is associated with excessive scar formation, it is conceivable that developmental programs could be utilized to resolve fibrotic tissue lesions.

3. The role of tubular epithelial cells in renal fibrosis

Several studies have demonstrated that tubular epithelial cells are the primary target of BMP7 in the kidney. BMP7 inhibits the secretion of proinflammatory chemokines by tubular epithelial cells [20] and reverses epithelial–mesenchymal transition, restoring tubular epithelial cell integrity [3]. These findings further highlight the central role of tubular epithelial cells in renal fibrogenesis. Whereas in the past, research has primarily focused on fibroblasts and inflammatory cells, tubular epithelial cells—the most abundant cell type in the kidney—should be increasingly considered as a therapeutic target.

4. The role of the extracellular matrix in renal fibrogenesis

An excessive deposition of extracellular matrix (ECM) is the prominent feature of renal fibrosis. ECM in general is conceived as a stable substance with minimal turnover, which provides structure to a given organ. Hence, previous strategies to reverse fibrosis centered around removing excessive ECM rather than regenerating cellular tissue constituents. Experimental studies that utilized recombinant BMP7 as an antifibrotic agent demonstrated that excessive ECM is resolved upon BMP7-mediated restoration of the cellular compartments [3]. These studies support the notion that fibrillar ECM undergoes a constant remodeling—just as cells do—and that restored cellular constituents can possibly rebuild their physiological ECM microenvironment.

5. Utilization of the BMP7 pathway for antifibrotic therapy

BMP7 is an endogenous growth factor that facilitates spontaneous repair of acute kidney injury. This preexisting BMP7 pathway can be utilized in animal models of CKD to facilitate repair of chronic renal fibrosis. This raises the possibility that the BMP7 pathway can be equally utilized to treat CKD in humans. However, one should be cautious, as this pathway, which is part of the kidney's physiological injury response, is highly complex and not fully understood. In view of the various agonists (ALK3, ALK6, BMPRII, KCP) and antagonists (gremlin, noggin, USAG-1) of BMP7 in the kidney, one must be aware that not all patients may be responsive to administered recombinant BMP7, and further understanding of BMP7 control mechanisms in health and disease are required. It is likely that levels of BMP receptor expression and expression levels of BMP antagonists determine responsiveness in an individual case.

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