**Translational Nephrology**

**Ramping up endogenous defences against chronic kidney disease**

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Bone morphogenic proteins (BMPs) are a group of glycoproteins that belong to the transforming growth factor beta superfamily. Of the several members expressed in the kidney, BMP-7 (known also as osteogenic protein-1) is of particular interest to nephrologists due to its critical role in branching morphogenesis during renal development and its ability to preserve tubular epithelial cell phenotype in the face of adversity, at least in experimental models [1]. The BMP-7 null mice die in the neonatal period in renal failure due to hypoplastic kidneys [2,3]. Even in the post-natal period, the distal tubules and collecting ducts continue to be a major site of BMP-7 synthesis [4]. Reduced expression has been reported in several renal diseases including ischaemic nephropathy, diabetic nephropathy, cyclosporine nephrotoxicity and 5/6 nephrectomy [5–9]. Intervention studies with recombinant BMP-7 first demonstrated salutary effects in animal models of acute renal failure and were followed by reports of reduced fibrosis in several chronic kidney disease models [9–14]. Although its renoprotective mechanisms of action are not fully elucidated, receptor-dependent effects on proximal tubular epithelium appear to be particularly important [12]. The BMP-7 transmits extracellular signals to nuclei by binding to BMP type II receptors (BMPR II) or the activin type II receptors (ActRIIa or ActRIIb) in conjunction with type I receptors [activin receptor-like kinase-2 (Alk2), Alk3 or Alk6], followed by activation of Smads 1, 5 and 8 and/or members of the mitogen-activated protein kinase family [15–17].

During renal injury, BMP-7 antagonizes transformation of renal tubular epithelial cell into fibroblast-like mesenchymal cells that are characterized by de novo synthesis of fibrillar collagens and enhanced overall matrix protein production (the process of epithelial-to-mesenchymal transition (EMT)). In experimental studies, these transformed cells can be identified phenotypically as cells that have lost E-cadherin and acquired α-smooth muscle actin (SMA) and/or fibroblast specific protein-1 (protein S100A4). When tubular basement membranes are degraded by proteases, such matrix metalloproteinases surviving transformed cells may take up residence in the interstitial space as activated (myo)fibroblasts and participate in scar formation. For unknown reasons, interstitial myofibroblasts appear to have other cellular origins, including resident interstitial fibroblasts or bone marrow-derived precursors and, at present, the relative contribution of the BMP-7-inhibitable EMT process remains controversial [18]. A particularly exciting finding is the potential for BMP-7 to reverse the EMT process, converting transdifferentiated mesenchyme-like tubular epithelium back to mature epithelial cells [19]. Achieving this effect in humans with chronic kidney disease could theoretically lay the groundwork to reverse fibrosis. The BMP-7 has been ascribed other biological functions that may also confer renoprotection, including significant anti-inflammatory effects [20,21].

Whether BMP-7 therapeutics will ever become a reality for human chronic kidney disease is unknown at this time. In addition to recombinant protein design and production challenges, there are other theoretical issues of concern. First, BMP-7 is a relatively small homodimeric peptide (~35 kDa) that is likely to be filtered in proteinuric renal diseases. Although not protective in a model of overload proteinuria possibly for this reason, BMP-7 did improve several parameters of renal injury in mouse models of Alport syndrome, anti-GBM nephritis and lupus nephritis [12,13,22]. Second, although BMP-7 receptors are expressed within the cortex (podocytes and proximal convoluted tubules) and medullary collecting ducts of normal rodents, little is known about receptor expression patterns in human renal diseases [23]. Third, given the relatively high endogenous levels of renal BMP-7, it stands to reason that exogenous BMP-7 would be...
most efficacious when endogenous production declines, another parameter that deserves further investigation, especially in chronic human kidney diseases.

An alternative therapeutic strategy might be to enhance the bioactivity of endogenous BMP-7. An exciting recent study by Yanagita et al. [24] suggests that such an approach offers promise. In their study, the role of uterine sensitization-associated gene-1 (USAG-1) was investigated in acute and chronic renal injury models. First identified in the uterus in 2002, USAG-1 became a candidate BMP antagonist based on bioinformatic data and its inhibitory effects in teeth (where it is also known as ectodin) [25,26]. Yanagita and colleagues [24] found that USAG-1 was highly expressed by distal tubules, in the same region that BMP-7 is produced. They generated USAG-1 knockout mice that were phenotypically normal, but demonstrated a remarkable degree of renal protection after cisplatinum-induced acute renal failure or unilateral ureteral obstruction. Two additional experiments suggested that renal injury attenuation in the USAG-1 null mice was at least partially mediated by enhanced BMP-7 signalling. First, in both models, levels of phosphorylated Smads 1, 5, and 8 were shown to be significantly higher in the USAG-1-deficient mice. Second, the benefit conferred by USAG-1 elimination was lost when BMP-7 was blocked with a neutralizing antibody.

**Fig. 1.** Nephron distribution of BMP-7, its antagonists and receptors. BMP-7 is normally expressed in medullary distal tubules and collecting ducts. BMP-7 has also been reported in the S3 segment of the proximal tubule and the thick ascending limb (TAL) of the loop of Henle. BMP-7 receptors are most abundant in the cortex (proximal tubules and podocytes) followed by collecting ducts. Several secreted BMP antagonists are also produced along the nephron. USAG-1 (uterine sensitization-associated gene-1) is most abundant, produced by distal tubules together with twisted granulation (Tsg). Three antagonists are concentrated in the inner medulla: DAN (differential screening-selected gene aberrative in neuroblastoma), PDRC (protein-related to DAN and Cerberus) and noggin. Chordin, coco and sclerostin are expressed at sites that are not yet clarified. Follistatin, an antagonist of activin A as well as BMP-7, is abundant in outer medullary tubules. Gremlin is not normally detected in normal kidneys, but it is induced in certain diseases (mesangial cells and tubules in diabetes). In contrast, KCP (kielin/chordin-like protein) enhances BMP-7 activity and is produced by proximal tubules. These data are based primarily on studies performed in animals.
Although, the number of apoptotic tubular cells and αSMA-positive interstitial cells were significantly reduced in the acute and chronic injury models, respectively, the benefit appeared far greater than can be explained by BMP-7-dependent tubular cell protection. For example, gene expression levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL1-β), monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor beta (TGF-β), and TGF-β, and the severity of interstitial inflammation were significantly reduced. It is also noteworthy that the changes in the renal cortex and proximal tubules were impressive, despite BMP-7 expression that is restricted to medullary tubules, and furthermore, BMP-7 mRNA levels were significantly reduced in the diseased kidneys compared to the non-injured kidneys. An alternative explanation deserves further consideration. Perhaps, USAG-1 potentiates renal injury and/or fibrosis independent of its BMP-7 inhibitory effects. Whether renal USAG-1 expression levels change with injury is not yet known. Although members of the cystine-knot family of BMP-7 antagonists such as USAG-1 are secreted proteins, thought to interact with ligands and block receptor binding sites [27], it is conceivable that some cystine-knot antagonists might interfere with other ligand–receptor pathways or even interact directly with currently unknown receptor(s). Indeed, USAG-1 may modulate Wnt signalling, another molecule that promotes fibrosis [28,29]. While USAG-1 appears to serve as a BMP-7 antagonist based on the available data from Yanagita [30] and other recent studies, the converse that BMP-7 might reciprocally serve as a molecular ‘trap’ for USAG-1 could also be true and needs to be further studied. Whatever its mode of action, it is clear that this interesting molecule plays a significant role in renal injury, both acute and chronic. We need to stay tuned as the story of USAG-1 continues to unfold.

But this is not the last chapter for BMP-7 in the kidney. A number of other proteins have been identified as BMP-7 agonists or antagonists, several of which are expressed in the kidney [7,30–33]. Most are members of the subfamily of cystine-knot proteins. Yanagita et al. [24] evaluated the renal expression of several of the known BMP antagonists. In their study, USAG-1 mRNA levels were the highest, but other antagonists were detected (Figure 1). Furthermore, Lin et al. [34] recently identified a protein they called kielin/chordin-like protein (KCP) that enhances BMP signalling. Unlike BMP-7 and USAG-1, KCP is expressed predominantly by proximal tubules. In a folic acid-induced acute injury model and in obstructive nephropathy, renal disease severity was significantly worse in KCP-null mice and was characterized by lower phospho-Smad1 levels consistent with reduced BMP-7 signalling activity.

What do these findings mean for clinicians? BMP-7 and its expanding family of regulatory proteins elicit several important responses when the kidney is damaged, either acutely or chronically. Although not discussed here, BMP-7 is also reported to antagonize vascular and bone disease, including lesions that develop at an accelerated rate in patients with chronic kidney disease [35–37]. While investigating the efficacy of recombinant BMP-7 therapy in human chronic kidney disease is theoretically attractive, we are reminded of various peptide therapies for acute renal failure, such as insulin-like growth factor-1, which has worked extremely well in rodent models but failed in humans [38,39]. Well-designed clinical trials will be critical. The growing list of BMP-7 regulatory proteins, such as USAG-1, offers an alternative approach for developing new renoprotective agents.

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References
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