Dogs Don’t Bark at Parked Cars

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Well, our term is up and it is time to move on. The owners have selected a new bench and we slowly fade into that good night. As I reflect on my 6 years as editor-in-chief, there are many highpoints in reporting new discoveries, but none compares with sharing the complexity of publishing with dedicated people; there is something inspiring about having worked with such a fabulous group of associate editors at JASN. Deeply in touch with every corner of nephrology, they taught all of us much about modern science.

Vivian Siegel, our executive editor, kept us on even keel, deftly navigating the art of best practices in editorship, style, and brinksmanship, particularly elevating the care one must show authors and reviewers. The magnificent tastes of Ray Harris and Sue Quaggin, our sequential deputy editors, guided me in sifting through nearly 7000 original submissions to find very best manuscripts for further review and publication. Our associate editors, Lloyd Cantley, Al George, Tom Coffman, Andy Rees, Bob Colvin, Terry Strom, Alp Ikizler, Mary Leonard, and Neil Powe, brought powerful and discriminating talent to complex fields of renal science and translational medicine. Jim Smith, our staff editor, wrote all of the highlights and rewrote titles and abstracts of original submissions to make our published material more readable, and Bonnie O’Brien, our ever-hovering managing editor, once again suffered patiently the painful training of novices for which we were eternally grateful.

All editors struggling for firmer footholds have a strange sense of inadequacy, and in our work we were no different. As a group, we set out to transform JASN in thoughtful ways, making the journal higher impact, more readable and crisp, and thinner to showcase the very best science to perspicacious readers. In the process, we hopefully succeeded in some small way in making JASN a pinnacle outlet for nephrology.

The unexpected challenge of editorship is finding attentive reviewers evenly split in their certainty over a particular manuscript and having to make a lonely decision. To the dismay of authors, we had no choice but to reject many good papers (including one of my own) in order to advance very best work. The adjudication of limited space by a journal editor, to paraphrase Holly Smith, is the art of providing an equitable distribution of poverty and gently nudging unhappy authors toward an equality of dissatisfaction, Talleyrand’s definition of diplomacy. In this I am sure we succeeded.

Our authors and dedicated reviewers provided us with many moments of sober reflection and sometimes mirth; my particular favorites of the latter were the unexpected arrival of a 138-page rebuttal letter to reviewer comments (don’t do that), the giddiness of receiving a startling new discovery in our inbox, initial submissions written in foreign languages, and summary conclusions over-reaching for that arcane transom of certainty. Likewise, many authors fretted over sharing more data supporting their very best ideas, forgetting the old axiom that if the ideas were really that good, one would still have to cram them down other people’s throats to gain acceptance.

There has been much debate in recent years whether science in nephrology is on the decline, and by extension, JASN is just the healthiest horse in the glue factory. I don’t agree. Everything we know about the kidney started somewhere in a laboratory, and nephrology is still a vast, provocative, and rich scientific discipline limited only by our ability to rapidly translate basic research to the bedside. More well-done clinical trials would clearly brighten our arc.

We wish Karl Nath and his new associate editors a prosperous journey into the future.

DISCLOSURES
None.

The Kielin/Chordin-Like Protein Checkpoint Constitutes a System of Checks and Balances in CKD

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Although in principle the kidney possesses a unique regenerative capacity, the physiologic repair response often gives way to a pathologic scarring process known as fibrogenesis, which leads to progressive loss of kidney function and subsequently to ESRD. The ultimate fate of the injured kidney is uniquely determined by the balance of two related growth factors, both of which belong to the TGF superfamily: TGF-β1 and bone morphogenic protein-7 (BMP-7).2

TGF-β1 is established as the prototypical profibrotic growth factor in the kidney and in other organs, such as the liver, lung, heart, or skin.3 Its prominent contribution to renal progression was highlighted by multiple studies documenting successful amelioration of experimental models of renal fibrosis upon administration of TGF-β1-neutralizing antibodies or soluble-receptor traps.3 Mechanistic studies linked the most relevant profibrotic cellular events, including fibroblast activation, epithelial-mesenchymal transition, and recruitment of fibrogenic macrophages to TGF-β1.1

The counterpart to TGF-β1 is BMP-7. BMP-7 is a prominent antifibrotic growth factor in the kidney and also in the aforementioned organs, including the heart and liver.4 Numerous studies demonstrate efficacy of administration of recombinant BMP-7 to inhibit progression of experimental renal fibrosis, and there is broad mechanistic evidence that BMP-7 targets profibrotic cellular events, including fibroblast activation, epithelial-mesenchymal transition, or endothelial-mesenchymal transition.5

The interplay of TGF-β1 and BMP-7 as determinants of kidney fate appears simple at first glance: TGF-β1 is profibrotic and BMP-7 is antifibrotic. In fibrosis, renal expression of TGF-β1 is increased, whereas BMP-7 expression is decreased. BMP-7 and TGF-β1 signaling directly counteract each other in their respective target cells.6 Not surprisingly, progression of experimental renal fibrosis can be ameliorated by direct inhibition of TGF-β1 or administration of recombinant BMP-7.

However, regulation of the activities of TGF-β1 and BMP-7 in the kidney is much more complex because the activities of both growth factors are controlled at multiple levels. In this context, the study by Soofi and coworkers in this issue of JASN provides new insights into how Kielin/chordin-like protein (KCP, a cystein-rich protein) affects the activities of both BMP-7 and TGF-β1, serving as a unique checkpoint in the fate decision of the injured kidney.7 Here we compare how activities of TGF-β1 and BMP-7 are regulated in the injured kidney and discuss how an understanding of mechanisms that control TGF-β1 and BMP-7 may lead to development of effective antifibrotic therapies in the future.

The TGF-β superfamily is a group of >30 cell regulatory proteins, which bind to specific pairs of so-called type I activin-like kinase receptors (ALKs) and type II serine/threonine kinase receptors.8 Upon ligand binding, the ALK receptor kinases then activate intracellular Smad proteins, which act as central signal messengers. TGF-β1 is the prototypical member of the TGF-β subfamily (consisting of TGF-β1, TGF-β2, and TGF-β3) that signals through binding to ALK5 receptors (and to lesser degree ALK1 and ALK4) and subsequently through Smad2 and Smad3 signaling molecules.8

BMP-7 belongs to the subfamily of bone morphogenic proteins (currently 16 members are known). BMP-7 signals through ALK3 receptors, as well as through ALK2 and ALK6, and subsequently through Smad1, Smad5, or Smad8 signaling molecules. Smad1/5/8-mediated BMP-7 signaling directly counteracts profibrotic TGF-β1-induced Smad2/3 signaling, serving as the molecular foundation for the antifibrotic activity of BMP-7.9 Within their respective TGF-β superfamily subgroups, TGF-β1 and BMP-7 are unique with regard to their activities in the context of fibrosis, even though they signal through various ALK receptors and Smad molecules as less effective family members.9 Such specific ligand-receptor activities are modulated, in part, through interactions with other extracellular proteins that are increasingly recognized as determinants of kidney fate.

For example, both TGF-β1 and BMP-7 are synthesized as inactive precursors, which require maturation through proteolytic cleavage of pro-domains before they elicit their biologic activities. In the case of TGF-β1, however, the mature peptide binds a latency associated peptide and latent TGF-β-binding protein, forming the inactive latent TGF-β complex.9 Thrombospondin-1, a matricellular glycoprotein, activates latent TGF-β, enhancing fibrogenesis. BMP-7 does not form such latent complex but is tightly regulated by extracellular proteins, which bind BMP-7 and affect its availability to bind specific receptors.9 Prominent examples include gremlin, noggin, CRIM1, USAG1, and follistatin, which bind BMP-7 and inhibit its interaction with ALK3 receptors.9 Their relevance is revealed in studies demonstrating, for example, that increased gremlin expression correlates with increased fibrosis in diabetic nephropathy or that experimental fibrosis is ameliorated in USAG1-deficient mice.10

In this context, the study by Soofi and coworkers highlights the role of the extracellular protein, KCP, in modulating the TGF-β1/BMP-7 balance.7 KCP, also known as CRIM2, NET67, cysteine-rich BMP regulator 2, and cysteine-rich motor neuron 2 protein, is a 160-kDa protein that contains 18 cysteine-rich domains and is abundantly expressed during kidney development. In the adult kidney, KCP is scarcely present, although levels of mRNA increase when kidneys are challenged in mouse models of renal fibrosis.11,12 The ability of KCP to regulate TGF-β1/BMP-7 balance is unique because it enhances BMP-7 signaling by facilitating binding to its principal receptor, ALK3, while blocking the binding of TGF-β1 to other ALK receptors.13 The study by Soofi and coworkers now corroborates the beneficial function of KCP by demonstrating the amelioration of renal fibrogenesis in mice that overexpress KCP in tubular epithelial cells.7 This finding is in line with
results of prior studies by this group, particularly those in KCP−/− mice; in the absence of congenital renal abnormalities, such null mice display increased susceptibilities to renal fibrosis.11 In summary, KCP is unique because it enhances BMP-7 activity (while other known extracellular modulators of BMP-7 activity serve as inhibitors) and because it also affects TGF-β1 activity.

The unique function of KCP as extracellular enhancer of BMP-7 activity is of particular interest in the context of existing challenges to translate the antifibrotic activity of BMP-7 into clinical use. Because production of recombinant BMP-7 in quantities needed for clinical use has been difficult, alternate strategies have been sought to exploit the undisputed antifibrotic activity of BMP-7 for clinical application. One successful approach has been development of synthetic peptides, which mimic antifibrotic activity of BMP-7 in the kidney while circumventing production challenges encountered with recombinant BMP-7;12 one such peptide (AA123) is being tested in a clinical trial.12

An alternate approach is to boost the renoprotective activity of endogenous BMP-7 in the kidney through stimulation of BMP-7 expression in the kidney, stimulation of Alk3 expression, or, as implied by the present study by Soo and coworkers, use of KCP as enhancer of endogenous BMP-7 activity. Although the size of KCP is prohibitive for potential use as a recombinant protein, further insights into interaction of KCP with BMP-7 and ALK3 may reveal novel avenues for clinical application of KCP mimetics in the future.

The study by Sooﬁ and coworkers reinforces the antifibrotic activity of BMP-7 signaling in CKD and may provide a novel approach to translating the protective role BMP-7 into clinical benefit.

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See related article, “Kielin/Chordin-Like Protein Attenuates both Acute and Chronic Renal Injury,” on pages 897–905.

Working Out Nephronophthisis Genetics One Family at a Time

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Congenital anomalies and cystic and hereditary nephropathies are among the most frequent causes of ESRD in childhood, adolescence, and early adulthood. Among these causes, nephronophthisis (NPHP) and related ciliopathies (NPHP-RCs) are a heterogeneous group of degenerative recessive diseases

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