tissue. In humans, chronic and acute ureteral obstruction can occur in various clinical situations, such as ureteral stone or ureteral carcinoma. Most published work examined PPAR-α levels in cell-line models, but none correlated PPAR-α levels in kidney tissue from patients with chronic obstructive nephropathy at various stages of development. Second, it is interesting that Boor *et al.*[3] discovered no significant differences in renal fibrosis between PPAR-α-deficient (PPAR-$\alpha^{-/-}$) and wild-type animals. Although the authors offer some reasonable explanations, these remain unsatisfying to explain the benefit of BAY PP1 therapy in chronic kidney disease, of which renal fibrosis is a major manifestation. It also raises the possibility that BAY PP1 may act partly through PPAR-independent pathways, depending on the model used, as has similarly been seen with other PPAR-α agonists.[9] Park *et al.*[10] induced diabetes in PPAR-α knockout mice and found increased profibrotic and proinflammatory effects; thus, more experiments with BAY PP1 might be needed in PPAR-α knockout animals, but with modifications to experimental conditions. Third, it would be interesting to conduct a time-course analysis in UUO models to determine possibly early progressive onset of PPAR-α expression.

In conclusion, the findings of Boor *et al.*[3] (summarized in Table 1) represent exciting work on a novel PPAR-α agonist, BAP PP1, that is potentially capable of ameliorating renal fibrosis and improving renal function. It would be unfair to compare the performance of BAY PP1 to that of other currently available PPAR-α agonists, as more research is needed for this assessment. Indeed, future studies should examine BAY PP1's safety and efficacy, as well as its molecular and cellular interactions. So, this Jedi needs to be curbed before it is ready to intervene against renal fibrosis.

DISCLOSURE

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Old friends form alliance against podocytes

Matias Simons[1,2,3] and Tobias B. Huber[2,4]

Wang and colleagues identify the activation of Wnt signaling as an important downstream event in transforming growth factor-β-mediated podocyte injury. Supported by other recent studies, canonical Wnt signaling is emerging as a critical stress pathway in podocytes and may be exploited for therapeutic strategies in the treatment of glomerulopathies.

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Animal development and homeostasis require a set of highly conserved cell-signaling pathways (including Wnt, transforming growth factor-β, Hedgehog, receptor tyrosine kinase (RTK), Notch, JAK/STAT, and mTOR) that are used repeatedly in different spatial and temporal contexts. In recent years, research has also focused on the cross-talk among these major signaling pathways. The cross-talk between the transforming growth factor-β (TGF-β)/bone morphogenetic protein (BMP) and Wnt pathways is probably the most extensively studied. The two pathways show strong interactions throughout the life of an animal, also on the molecular level. TGF-β/BMP and Wnt proteins are secreted ligands that form overlapping extracellular gradients during embryonic development. In the *Drosophila* wing disc, for example, the concerted action of orthogonal gradients of Wg and a member of the TGF-β family of secreted factors, Decapentaplegic (Dpp), determines the shape of the wing. Also in the responding cells, a number of cytoplasmic interactions between components of these pathways fine-tune their respective signaling. The hot spot of TGF-β/Wnt cross-talk, however, is the nucleus. β-catenin and Lef1/Tcf, which are downstream

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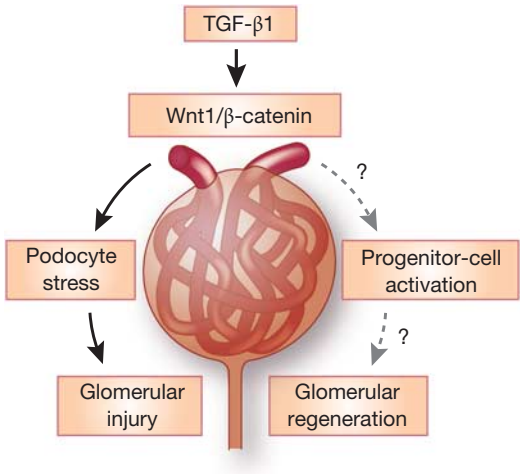

Figure 1 | TGF-b1-mediated activation of Wnt signaling leads to podocyte stress and injury. One hypothetical reason for reactivation of this developmental pathway could be the stimulation of progenitor cells for glomerular regeneration. A similar balance between podocyte death and repair has recently been shown for the Notch pathway.

components of the Wnt signaling cascade, can form a complex with the TGF-β signaling transducer Smad to synergistically regulate gene expression. This is best illustrated in the Spemann's organizer of *Xenopus laevis*, another famous example in developmental biology.[1] In some contexts, the two pathways can also show antagonistic behavior. While the Wnt pathway often orchestrates mesenchymal–epithelial transition, such as in the developing kidney during metanephric mesoderm induction, TGF-β signaling is known to promote the conversion of epithelia to mesenchyme in fibrotic events.

Wang *et al.*[2] (this issue) report on how TGF-β signaling and Wnt signaling interact in podocytes. Interestingly, both pathways have independently been identified as key factors in the progression of glomerular failure. Increased TGF-β activity in podocytes, typically, leads to apoptosis and/or detachment of podocytes from the glomerular basement membrane, initiating the development of glomerulosclerosis. Podocyte cell death seems to be mediated by a number of different TGF-β-dependent pathways, including nuclear factor-κB inhibition[3] and Notch activation.[4] The article by Wang *et al.*[2] now adds another important downstream event to the TGF-β signaling node in the podocyte. The authors demonstrate that several Wnts, in particular Wnt1, are upregulated in response to ectopic expression of TGF-β1, which subsequently leads to β-catenin activation. Importantly, the Wnt antagonist Dkk1 is effective in blocking TGF-β1-mediated β-catenin activation *in vivo*, resulting in diminished podocyte injury and albuminuria. These findings are highly relevant to human glomerular disease, as upregulated Wnt expression has been associated with diabetic nephropathy and focal segmental glomerulosclerosis.[5,6] Consistent with these findings, several recent studies demonstrated that the genetic or pharmacological inhibition of Wnt/β-catenin signaling ameliorates glomerular disease.[5–7]

Most of the major signaling pathways are vital during the early stages of glomerular development, when nascent cells acquire their identities to organize kidney architecture. However, the same pathways seem to interfere with the later function of mature podocytes. Recent examples of such a failed 'compensatory attempt' of developmental programs during glomerular injury are deregulated mTOR,[8,9] Notch,[4] and Wnt signaling in podocytes. Therefore, it could indeed be a key feature of podocyte injury that developmental programs are being reactivated in glomerular diseases. The effect on podocyte behavior is still rather unclear in this context. Wang *et al.*[2] demonstrate that enhanced Wnt signaling in adult podocytes leads to the upregulation of mesenchymal markers as well as a ownregulation of nephrin expression. In another recent study, it was shown that loss of Wnt signaling enhanced podocyte adhesiveness and differentiation.[6] Therefore, canonical Wnt signaling seems to promote a dedifferentiated and more mesenchymal podocyte phenotype, resulting in the inability of the adult podocyte to maintain the complex three-dimensional architecture of the filtration barrier. In the kidney, the tuning down of Wnt signaling during development and differentiation is critical not only in the glomerulus but also for terminal differentiation of tubular epithelial cells and the prevention of overproliferation of kidney tubules and polycystic kidney disease.[10]

But why is the glomerulus reviving potentially harmful developmental programs in response to injury? A possible explanation may be that these programs control the proliferation of glomerular progenitor cells. In this respect, it has been shown that Notch activation stimulates renal progenitors, while a downregulation of the Notch pathway is required for their specification toward the podocyte lineage.[11] Renal progenitors of the glomerulus can be found within the parietal epithelium of the Bowman's capsule. Consistent with this, the immunohistochemical analysis by Wang *et al.*[2] seems to show upregulated Wnt1 expression not only in the podocyte (in response to TGF-β), but also in the parietal cells.[2] Apart from Notch, Wnt is also a prominent player in stem-cell control and vertebrate regeneration. Thus, a glomerulus-wide increase in Wnt1 after injury might promote repair processes via the progenitor cells but at the same time harm the adult podocytes by causing their detachment and dedifferentiation (Figure 1).

In summary, the study by Wang *et al.*[2] emphasizes once again the importance of the Wnt pathway in the podocyte as well as the inhibition of Wnt signaling as a potential therapeutic strategy in glomerular disease. The study also introduces a novel pathway for Wnt activation. This time, activation is via an old friend—TGF-β.

DISCLOSURE
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Blockade of PDGF receptor signaling reduces myofibroblast number and attenuates renal fibrosis

Valerie S. LeBleu[1] and Raghu Kalluri[1,2,3]

Fibrosis can be considered as wound healing that never ceases, and activated fibroblasts (myofibroblasts) probably play a critical role in this unabated tissue repair process. In the setting of renal fibrosis, two central questions remain unanswered: Where do activated myofibroblasts come from; and what mechanism or mechanisms keep them activated? The study by Chen and colleagues addresses the role of platelet-derived growth factor receptor (PDGFR) signaling in the activation of myofibroblasts.

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Fibrosis can be considered as wound healing that never ceases. In the setting of tissue repair, myofibroblasts appear in conjunction with inflammatory response to provide the required physical and biochemical support to enable regeneration, upon which all repair activities come to a halt with the disappearance of activated myofibroblasts and inflammation. In the kidney, acute injury is associated with such plastic response, whereas in the chronic injury setting, the resolution phase associated with such regenerative process is impaired, resulting in unabated repair that leads to what is referred to as fibrosis. Although many key questions remain unanswered with regard to the mechanism behind organ fibrosis, the kidney is offering an excellent model system to systematically probe them. Two central questions that remain are: Where do activated fibroblasts (myofibroblasts) come from; and what mechanism or mechanisms keep them activated? In the study by Chen and colleagues[1] (this issue), the role of platelet-derived growth factor receptor (PDGFR) signaling in the activation of myofibroblasts is addressed.

Chen and colleagues[1] demonstrate that altered PDGF–PDGFR signaling is associated with kidney fibrosis, and provide compelling evidence for the role of PDGFR signaling in myofibroblast activation. Although the total number of PDGFRβ/α^+ cells (presumably interstitial cells) was not quantified in this study, the authors clearly demonstrate an increase in expression of specific components of the PDGF–PDGFR signaling axis in renal fibrosis, with a robust increase in PDGF-A through PDGF-D and PDGFRβ and PDGFRα. The use of anti-PDGFRα (1E10) and anti-PDGFRβ (2C5) antibodies from ImClone Systems reduces the observed increase in PDGF and PDGFR gene expression in mouse fibrotic kidney and subsequently reduces the activation of PDGFRα and PDGFRβ. By this approach, a marked decrease in the number of α-smooth muscle actin-positive (αSMA^+) interstitial myofibroblasts and overall COL1A1 and COL3A1 gene expression is noted. The authors suggest that impaired macrophage recruitment due to diminished PDGFRα/β signaling with the use of anti-PDGFRα/β antibodies, as well as imatinib mesylate (which also targets PDGFRβ signaling), improves renal fibrosis. This study by Chen and colleagues[1] is supported by published findings of Wang and colleagues[2] which showed that imatinib mesylate might reduce renal fibrosis in unilateral ureteric obstruction in mice, and also by the studies by Lassila and colleagues[3] using mice with diabetic nephropathy. Together these studies raise the interesting possibility that targeting PDGFR signaling might offer new therapeutic avenues for renal fibrosis, perhaps by reducing macrophage infiltration.

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