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Review

Wnt signaling in kidney tubulointerstitium during disease

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Summary. The evolutionary conserved Wnt signaling transduction pathway plays essential roles in a wide array of biologic processes including embryonic development, branching morphogenesis, proliferation and carcinogenesis. Over the past ten years it has become increasingly clear that Wnt signaling also regulates the response of adult organs to disease processes, including kidney disease. This review will focus on the growing literature implicating important roles for Wnt signaling during disease in two separate kidney compartments: the tubular epithelium and the interstitium.

Key words: Kidny injury, Fibrosis, Wnt, β-catenin, Myofobroblast

Principles of Wnt signaling

The term Wnt combines the names of two genes; the murine integration-1 gene (Int) and Drosophila Wingless (Wg) that were ultimately discovered to be homologues. Wnt thus stands for "Wingless-related integration site" (Nusse et al., 1984; Rijsewijk et al., 1987). The Wnt receptor is a heterodimeric complex consisting of Frizzled (Fzd) and LDL-related protein (LRP5/6). When the Fzd/LRP complex is not engaged, the serine-threonine kinase glycogen synthase kinase 3β (GSK3β) constitutively phosphorylates the transcriptional coactivator β-catenin (Nusse et al., 1984). This complex includes Axin and the tumor suppressor protein, adenomatosis polyposis coli (APC) which together regulate cytoplasmic β-catenin destruction (Aberle et al., 1997).

19 different Wnt proteins and 10 various Frizzled (Fzd) receptors have been identified in the mouse (Moon et al., 2004). Wnt ligands are all secreted lipid-modified glycoproteins that can trigger either canonical or non-canonical pathway activation upon receptor binding. Evenness interrupted (EVI) is a transmembrane protein that is vital for the secretion of all canonical and noncanonical Wnt ligands (Banziger et al., 2006; Bartscherer et al., 2006). Canonical Wnt signaling leads to binding of Axin to the cytoplasmic tail of LRP6 at the plasma membrane (Mao et al., 2001). This inhibits destruction complex activity, leading to accumulation of β-catenin with subsequent translocation to the nucleus (Li et al., 2012). Tankyrases stimulate the proteosomal degradation of Axin2, thereby inhibiting β-catenin destruction and augementing forward canonical Wnt signaling (Huang et al., 2009). Once in the nucleus, β-catenin forms a complex with members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors, which in turn recruits other co-factors like cyclic AMP response-element binding protein (CREB) binding protein (CBP), p300, TNIK (TRAF2 and NCK Interacting Kinase), and ultimately induces the transcription of Wnt/ β-catenin pathway target genes (Bilic et al., 2007).

An additional level of control of Wnt signaling lies with secretion of Wnt antagonists that can either bind and sequester Wnt ligand or bind the receptor and block

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ligand binding (Kawano and Kypta, 2003). Members of the secreted Frizzled-related protein (sFRP) family and Wnt Inhibitory Factor-1 (WIF-1) act as decoy receptors that bind to Wnt ligands to prevent their interaction with Fzd/LRP receptor-complex (Bafico et al., 1999; Finch et al., 1997; Hsieh et al., 1999). Klotho is a single-transmembrane protein whose extracellular domain can be spliced and released into circulation to bind certain circulating ligands, like Wnt (Imura et al., 2007), and inhibit its activity (Liu et al., 2007). The Dickkopf (Dkk) proteins family by contrast (Bafico et al., 2001) binds directly to LRP 5/6, preventing the formation of active signaling complex Wnt-Fzd-LRP5/6 (Sakane et al., 2010).

Role of Wnt in kidney development

Kidney development in mouse begins at E10.5 at the caudal end of the nephric duct. A prespecified group of nephrogenic cells called the metanephric mesenchyme (MM) induce an outgrowth from the nephric duct called the ureteric bud (UB) that then invades the MM. These two cell types then undergo reciprocally inductive interactions culminating in formation of individual nephrons through branching of the UB.

The UB forms a T-shaped bifurcation at E11.5, and then goes through several cycles of branching and elongation to generate the metanephric collecting duct system (Cebrian et al., 2004). During this process, each UB tip is surrounded by a cap of MM, a subset of which gives rise to nephron progenitors that proliferate, differentiate into glomerular and tubular epithelial cells, and fuse with the collecting duct. Decades ago studies illustrated the essential role of reciprocal and inductive signaling between the UB and the MM in initiating and maintaining the cycles of UB branching and nephron induction that trigger the formation of the metanephros (Grobstein, 1956).

Herzlinger et al. first showed that Wnt1-expressing NIH3T3 cells induced tubule formation when co-cultured with metanephric blastemata, indicating a role for the Wnt pathway in mammalian nephrogenesis (Herzlinger et al., 1994). Later, McMahon showed that NIH3T3 cells expressing many different Wnts including Wnt1, Wnt3a, Wnt4, Wnt7a, and Wnt7b could all induce tubule formation when co-cultured with metanephric mesenchyme (Kispert et al., 1998). Another group showed that canonical Wnt signaling is sufficient to induce tubule-formation in mesenchymal extracts (Kuure et al., 2007). Collectively, these experiments demonstrated that Wnt signaling induces epithelialization from metanephric mesenchyme precursors. A critical role for β-catenin in tubule differentiation from MM was shown in experiments where β-catenin was genetically stabilized in the MM. In this experiment, mesenchyme isolated at E11 formed tubules in culture in the absence of an inducing agent, indicating that canonical Wnt signaling is required for nephron differentiation (Kuure et al., 2007). In complementary studies, Carroll showed that β-catenin is both necessary and sufficient for the expression of target genes of both self-renewing and differentiating progenitor cells (Karner et al., 2011). Consistent with these findings, Iglesias et al used a Wnt-reporter line to show that canonical Wnt signaling is initially active throughout the mesonephric duct and UB. As nephrogenesis halts, the canonical Wnt signaling is downregulated (Iglesias et al., 2007).

Wnt9b from the UB signals to MM, directing both self-renewal and differentiation (Karner et al., 2011). $Wnt9b^{-/-}$ embryos fail to induce Wnt4 in the pre-tubular aggregate, halting nephrogenesis (Carroll et al., 2005). Another target of Wnt9b is the transcription factor Six-2 which is required for MM self-renewal. Recent experiments have revealed a role for stromal fibroblasts in amplifying the UB-derived Wnt9b signal via a Fat4-dependent mechanism (Das et al., 2013). Ablation of stroma during nephrogenesis resulted in markedly decreased expression of pre-tubular aggregate gene targets, suggesting that signaling from the cortical stroma promotes differentiation of the progenitor cells, not self-renewal (Das et al., 2013). After metanephric mesenchyme condenses to form a pretubular aggregate, these cells express Wnt4 which is required for further epithelial maturation (Das et al., 2013). For example, $Wnt4^{-/-}$ pups die within 24 hrs of birth and their kidneys fail to form pretubular aggregates (Stark et al., 1994). Grouls et al deleted canonical Wnt signaling in epithelial cells at the late S-shaped body stage using Pax8Cre transgenic mice. The kidneys of these mutant mice were hypoplastic with a thin cortex and small underdeveloped capillary tufts. This demonstrated that the canonical Wnt signaling has an essential role in the post-inductive stages of nephron development and glomerular formation (Grouls et al., 2012).

Wnt signaling plays roles in nephron maturation as well. Deletion of Wnt7b from collecting duct caused a failure of medullary tubules to develop (Yu et al., 2009). Interestingly, removal of β-catenin from the interstitium phenocopies mice lacking Wnt7b in the collecting duct, suggesting a model whereby collecting duct-derived Wnt7b signals to the interstitial cells of the mesenchyme, activating canonical Wnt signaling, which leads to poorly defined downstream signals that act in a paracrine fashion on medullary epithelia (Yu et al., 2009). A summary of known roles for Wnt ligands during kidney development appears in Fig. 1.

Wnt Signaling in epithelial cells in injury

After nephrogenesis is complete, Wnt signaling is downregulated and remains largely quiescent in adult kidney (Costantini and Kopan, 2010; Hendry et al., 2011; Stark et al., 1994; Taguchi et al., 2014). After injury, however, Wnt signaling is reactivated (Nelson et al., 2011). The expression domain of Wnt ligands and responding cells after injury varies considerably. During homeostasis, Wnt pathway reporters suggest that the

renal papilla is the only site of active canonical Wnt signaling (Itaranta et al., 2006; Liu et al., 2009). Consistent with this, we have observed strong Wnt4 expression in papillary collecting duct (but not cortical collecting duct) of adult mouse kidney (DiRocco et al., 2013). After kidney injury, Wnt canonical pathway activation can be detected in cortex, particularly tubular epithelial cells (Lin et al., 2010). Importantly, however, active Wnt signaling is also detected in the interstitium using a more sensitive reporter (Ren et al., 2013).

Several reports suggest that canonical Wnt-β-catenin activation in injured tubular epithelial cells promotes epithelial repair. β-catenin is clearly upregulated in tubular cells in injured kidney (He et al., 2009; Zhou et al., 2012, 2013a). Wang and colleagues reported that β-catenin promotes survival of renal tubular cells through inhibition of pro-apoptotic Bax expression (Wang et al., 2009; Zhou et al., 2012). Consistent with this, tubule-specific ablation of β-catenin aggravates the intensity of acute kidney injury (Zhou et al., 2012). Conversely, tubule-specific deletion of β-catenin did not affect renal interstitial fibrosis in a unilateral uretral obstruction (UUO) model, possibly by diminished expression of matrix metalloproteinase 7 (MMP-7) (Zhou et al., 2013a). The same group has previously shown that MMP-7 levels correlate with Wnt/β-catenin activity in a UUO model (He et al., 2012). On the other hand, continued activation of the Wnt/β-catenin pathway in tubular cells results in maladaptive repair. Two groups have shown that constitutive activation of the Wnt pathway in tubular cells in different models of CKD and AKI in mice promote kidney injury, where decreased Klotho expression cause sustained Wnt/β-catenin activation (Satoh et al., 2012; Zhou et al., 2013b).

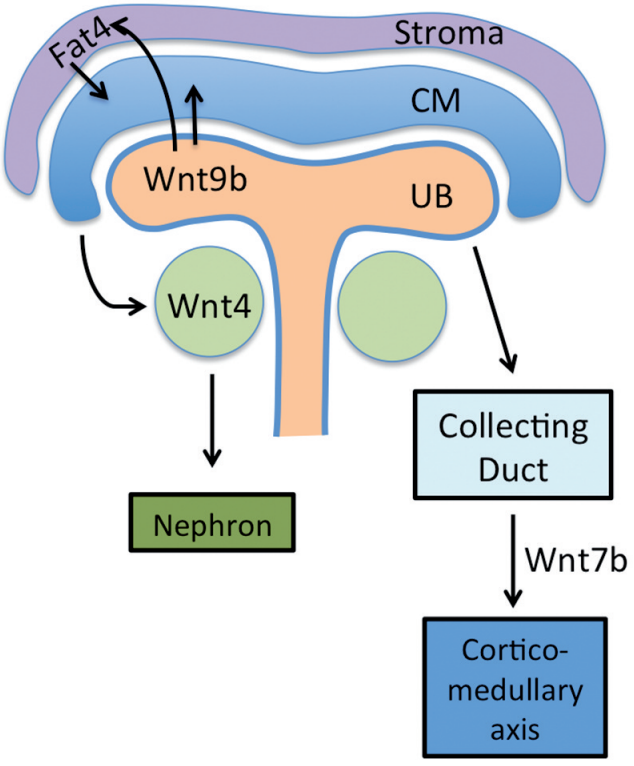

Fig. 1. Wnt signaling during nephrogenesis. The ureteric bud (UB) secretes Wnt9b that signals to the cap mesenchyme (CM) to either self-renew or differentiate. In addition, Wnt9b signals to stroma surrounding CM where a Fat4-dependent mechanism amplifies the Wnt9b signal to differentiating CM. As cap mesenchyme condenses to form the pretubular aggregate, Wnt4 is expressed which is required for mesenchyme to epithelial transition. The pretubular aggregate differentiates into renal vesicle, and ultimately the nephron. UB develops into collecting duct, and collecting duct-derived Wnt7b regulates cortico-medullary axis patterning.

There are few published descriptions of non-canonical Wnt signaling in tubular epithelium after injury. Zhang and colleagues recently showed that TGF-β induces autocrine Wnt11 expression and signaling in primary cultured proximal tubule cells. Induced Wnt11 subsequently activates mesenchymal gene expression in these cells through non-canonical Wnt signaling (Zhang et al., 2012). Specifically, Wnt11 activates the c-Jun N-terminal kinase (JNK) pathway. TGF-β, Wnt11, and JNK were also all activated in a UUO model suggesting this signaling pathway is also active *in vivo*. This paper is important because it shows that not only do injured tubular epithelia respond to Wnt ligands, but they also secrete Wnt ligands in response to injury.

The sources of Wnt ligands that drive tubular canonical and non-canonical Wnt signaling have been only partially defined. Duffield has shown that macrophages deliver Wnt7b in a paracrine fashion to injured epithelia after AKI (Lin et al., 2010). Whether or not downregulation of Wnt-inhibitory proteins might also underlie some of the pathway activation observed in the postischemic kidney is unclear, but a distinct possibility by extension from what is observed in other organs. For example, TGFβ, strongly associated with renal fibrosis, is markedly increased in all diabetic nephropathy animal models as well as human biopsies of diabetic nephropathy (Yamamoto et al., 1993) (reviewed in (Sakharova et al., 2001)). Mice that overexpress TGFβ (Kopp et al., 1996) or are given exogenous TGFβ (Ledbetter et al., 2000) develop renal fibrosis. Antibodies against either TGFβ (Border et al., 1990) or its receptor (Kasuga et al., 2001) reduce fibrotic disease including in animal models of diabetic nephropathy (Ziyadeh et al., 2000), as does genetic deletion of the TGFβ effector Smad3 (Inazaki et al., 2004; Sato et al., 2003). In skin, TGFβ is known to reduce expression of the Wnt antagonist Dickkopf-1, which activates Wnt signaling and promotes fibrosis (Akhmetshina et al., 2012).

Zhou et al. showed that normal kidney highly expressed Klotho, an endogenous antagonist of Wnt signaling, in tubular epithelium, and decreased Klotho levels in injured kidney increased β-catenin, which might accelerate fibrogenesis (Zhou et al., 2013b). They

also showed that TGFβ suppressed Klotho expression and Klotho overexpression abolished the fibrogenic effect of TGFβ. The downregulation of other Wnt-inhibitory proteins might also regulate the Wnt signaling (Koch et al., 2011; Sun et al., 2014).

Wnt signaling in kidney interstitium after injury

Chronic kidney disease (CKD), defined as loss of kidney function for more than three months, is characterized pathologically by interstitial fibrosis and tubular atrophy (IFTA) in addition to glomerulosclerosis, peritubular capillary rarefaction, and inflammation (Grgic et al., 2012). In CKD, there is accumulation of myofibroblasts and macrophages in the interstitium, (Becker and Hewitson, 2000; Farris and Colvin, 2012), resulting in excessive ECM deposition (Lin et al., 2008). After chronic kidney injury, there is strong activation of Wnt signaling in kidney (Fig. 2). Both myofibroblast activation and macrophage recruitment are important aspects of kidney fibrosis and Wnt signaling in each interstitial cell type will be reviewed here.

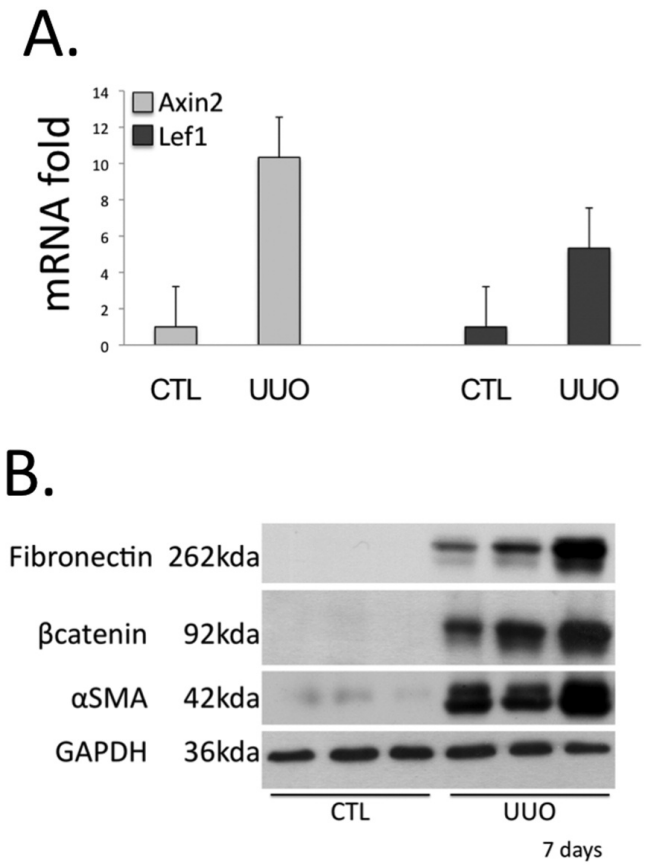

Fig. 2. The canonical Wnt pathway is activated during kidney fibrosis. **A.** Transcripts of canonical Wnt pathway target genes Axin2 and Lef1 increase 7 days after unilateral ureteral obstruction, a fibrosis model. **B.** Levels of stabilized β-catenin protein are substantially increased in fibrotic (UUO) kidneys compared to control. An increase in fibrotic read-outs (αSMA and fibronectin) is commensurate with the rise in stabilized β-catenin 7 days after UUO.

Interstitial fibroblasts

Using TCF/LEF:H2B-GFP transgenic mice, Ren et al have demonstrated that interstitial fibroblasts and pericytes respond to kidney injury with activation of the canonical Wnt/ β-catenin pathway (Ren et al., 2013). The increase in the canonical Wnt signaling *in vivo* after injury is noted to be greater in the pericyte/myofibroblast population than in the epithelial compartment. In a UUO renal fibrosis model, inhibiting the Wnt pathway with Dkk1 reduced pericyte transition and the subsequent fibrotic phenotype. In an attempt to find possible cross talk between the Wnt pathway and other profibrotic ligands, Ren et al also demonstrated that PDGF-BB induces proliferation while TGFβ and CTGF promote migration of kidney pericytes *in vitro* through direct LRP-6 activation independent of canonical Wnt signaling. Thus, Wnt ligand engagement of LRP-6 is vital for the transduction of the pro-fibrotic signal activating pericytes into myofibroblasts.

A substantial literature implicates activation of Wnt signaling in stroma of non-renal organs as well. Biopsies of fibrotic organs from human subjects with either systemic sclerosis, interstitial pulmonary fibrosis or liver cirrhosis reveal an active canonical Wnt pathway in fibroblasts (Akhmetshina et al., 2012; Beyer et al., 2012; Lam et al., 2011; Wei et al., 2012). Beyer et al generated a transgenic mouse where β-catenin is constitutively stabilized in skin fibroblasts which led to the rapid development of fibrosis within 2 weeks with dermal thickening, accumulation of collagen and differentiation of resting fibroblasts into myofibroblasts (Beyer et al., 2012). The same group also over expressed Wnt10a in mouse skin fibroblasts which resulted in skin fibrosis (Akhmetshina et al., 2012). Using the same genetic approach, mice constitutively expressing a Wnt inhibitor, Dkk1, in fibroblasts were resistant to bleomycin-induced skin fibrosis (Akhmetshina et al., 2012). However, the addition of TGF- β both *in vitro* and *in vivo* activated the canonical Wnt pathway in fibroblasts by inhibiting Dkk1. Finally, the transgenic mice constitutively expressing Dkk1 in skin fibroblasts, were resistant to local fibrosis after the injection of adenovirus Ad-TBRI^{act}, a TGFβ-inducer. This highlights a crosstalk between both pathways in the pathogenesis of fibrotic diseases (Akhmetshina et al., 2012). Wei et al revealed an alternative interaction between the TGF-β and canonical Wnt pathways in models of fibrosis. They stimulated explanted human skin mesenchymal cells with Wnt3a which induced β-catenin activation and led to smad-dependent profibrotic response and myofibroblast differentiation through autocrine TGFβ signaling (Wei et al., 2012). Lam et al showed that the canonical Wnt pathway in lung fibroblasts promotes proliferation and migration but not ECM production and myofibroblast differentiation (Lam et al., 2011).

Persistent activation of the canonical Wnt signaling in interstitial fibroblasts thus leads to increased myofiblast transition, ECM deposition, and exaggerated fibrotic phenotype.

We have shown that chronic kidney injury causes induction of Wnt4 in kidney medullary interstitial fibroblasts (DiRocco et al., 2013). However, deletion of Wnt4 in kidney stroma had no baseline phenotype, nor did it reduce the severity of fibrosis. In fact, β-catenin levels were elevated in both wild-type and Wnt4 null kidneys, suggesting that other Wnt ligands compensated for the absence of Wnt4 (He et al., 2009; Moon et al., 2004). Consistent with this possibility, constitutive activation of canonical Wnt signaling in renal stroma led to spontaneous myofibroblast differentiation (DiRocco et al., 2013). One of the lessons of this study is that interfering with the Wnt pathway at the level of ligands may not be an effective therapeutic strategy for the development of anti-fibrotic therapies, since there is redundancy with multiple Wnt ligands induced after chronic injury.

Interstitial macrophages

In human kidney biopsies, there is a correlation between the infiltration of macrophages, the degree of fibrosis and the ensuing progression of CKD to ESRD (Becker and Hewitson, 2000; Bohle et al., 1996). In models of kidney fibrosis, tubulointerstitial macrophage recruitment is markedly increased (Diamond, 1995; Schreiner et al., 1988). Many groups have shown that blockade of macrophage recruitment in renal fibrosis models ameliorates tubulointerstitial injury (Lange-Sperandio et al., 2002; Ophascharoensuk et al., 1999) and decreases fibrosis (Henderson et al., 2008; Lin et al., 2009).

In kidney development, Wnt7b plays a crucial role in regulating epithelial cell differentiation, proliferation and polarization (Kawakami et al., 2013). Little is known about the role of Wnt signaling in macrophage recruitment or epithelial repair processes. Lin et al has genetically deleted Wnt7b in macrophages using the *Csf1r-Cre;Wnt7b*$^{flox/-}$ transgenic mice, and showed that these mice had delayed kidney recovery after injury (Lin et al., 2010). They also showed a beneficial effect of M2 macrophage producing Wnt7b which resulted in epithelial cell progression in its cell cycle and restoration of the tubular basement membrane (Lin et al., 2010). During kidney repair, macrophages migrate around injured tubules during the regenerative phase to aid in epithelial cell recovery. Another recent report revealed a correlation between decreased recruitment of macrophages and the fibrotic response, where kidneys with less fibrosis and lower macrophage abundance had higher Wnt4 protein (Villanueva et al., 2014).

The role of canonical Wnt signaling in macrophages

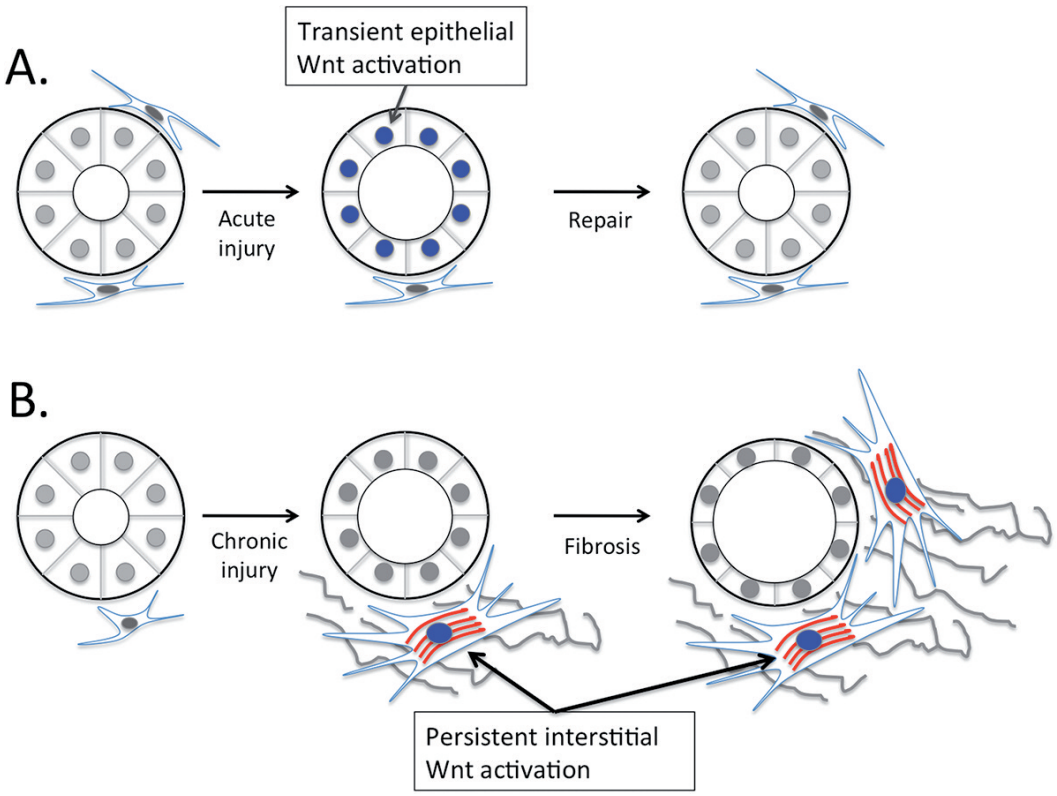

Fig. 3. Opposing effects of Wnt signaling in kidney epithelial vs. interstitial compartments in acute vs. chronic injury. **A.** Transient activation of the canonical Wnt pathway in the epithelial compartment promotes appropriate healing and repair. This repair can result in the restoration of both structure and function that is similar to normal state. **B.** Persistent activation of the Wnt pathway in the interstitial compartment leads to fibrotic changes and prevents normal repair. Unrestrained canonical Wnt signaling within stroma leads to chronic kidney disease and kidney failure.

is also evident in other organs leading to fibrosis and increased tissue contractility. In Dupuytren's disease, progressive fibrosis of the palms, significant numbers of activated pro-inflammatory M1 macrophages were present in myofibroblast-rich inflammatory nodules (Verjee et al., 2013). These nodules had abundant pro-inflammatory cytokines, including tumor necrosis factor (TNF), likely originating from pro-inflammatory M1 macrophages. Palmar fibroblasts of Dupuytren's patient's respond to TNF via canonical Wnt activation (Verjee et al., 2013).

Duchenne muscular dystrophy (DMD) is a skeletal muscle disorder that leads to tissue fibrosis. Matrix metalloproteinases (MMPs) are involved in tissue remodeling, inflammation, and development of interstitial fibrosis. Inhibition of MMP-9 reduces the M1 macrophage fraction while augmenting the M2 phenotype presence. This inhibition leads to enhanced canonical Wnt signaling and improved engraftment of transplanted myoblasts (Hindi et al., 2013). Future research is warranted to investigate the significance of Wnt signaling in the determination of the fate of recruited macrophages in areas of injury.

Therapeutic prospects

Fibrotic kidneys display aberrant activation of canonical Wnt signaling making this a potential pathway for anti-fibrotic therapy. Dismantling the β-catenin-cyclic AMP response-element binding protein (CREB) binding protein (CBP) complex is an attractive option to restrain hyperactive β-catenin signaling. ICG-001 binds to CBP competitively and can prevent β-catenin/CBP transcription complex formation (Eguchi et al., 2005; Ma et al., 2005). In a UUO model of kidney fibrosis, Hao et al were able to attenuate kidney interstitial fibrosis by IP injections of ICG-001. Late administration of ICG-001 was also effective in mitigating the fibrotic response in the same UUO model, where the drug was injected 3 days after inducing UUO (Hao et al., 2011). He et al delivered Dkk1 gene, a Wnt antagonist, in mice with UUO injury and this led to significant reduction in renal β-catenin and target gene expression. They demonstrated inhibition of myofibroblast activation; suppressed expression of fibroblast-specific protein 1, type I collagen, and fibronectin; and reduced total collagen content in this obstructive nephropathy model (He et al., 2009). In their studies, Ren et al show that the soluble protein Dkk1 and its receptor LRP-6 are important regulators in activating resident fibroblast into matrix producing myofibroblasts (Ren et al., 2013). They also show that this effect, although dependent on Wnt signaling, is independent of its canonical pathway (Ren et al., 2013). Distler et al attempted to inhibit the canonical Wnt pathway in mouse models of skin fibrosis induced by either bleomycin or adenoviral overexpression of a constitutively active TGFβ receptor I (Ad-TBRI) (Distler et al., 2013). XAV939 is a Tankyrase inhibitor that stabilzes the β-catenin destruction complex and selectively inhibits the canonical Wnt pathway (Huang et al., 2009). Using XAV939, they illustrated an antifibrotic effect with reduced collagen accumulation and myofibroblast transition (Distler et al., 2013). Using the same transgenic mice, the same investigators inhibited both canonical and non-canonical Wnt pathways using a knock-down of EVI, effectively diminishing the fibrotic response (Distler et al., 2014).

Vitamin D analogues have some potential as Wnt antagonizing drugs. In some contexts, they inhibit β-catenin signaling either by sequestering β-catenin through binding to the vitamin D receptor (Palmer et al., 2001) or through β-catenin nuclear export and re-localization to the membrane at its E-cadherin site (Larriba et al., 2007). Activated vitamin D can also inhibit β-catenin signaling by inducing the expression of Dkk1 (Pendas-Franco et al., 2008). He et al show that paricalcitol, a vitamin D analog, attenuates fibrotic response when they analyzed the mice 5 weeks after adriamycin injection (He et al., 2011). They found that paricalcitol inhibits the renal expression of multiple Wnts, like Wnt4, Wnt7a, Wnt7b, and Wnt10a. Their data suggest that paricalcitol treatment decreases the expression and nuclear localization of β-catenin in epithelial cells after injury (He et al., 2011).

Loss of Klotho might promote kidney injury by constitutive activation of the Wnt pathway (Satoh et al., 2012; Zhou et al., 2013a). Zhou et al intravenously injected an expression vector of the secreted form of Klotho (pV5-sKlotho) through hydrodynamic-based gene delivery at day1 (as a preventive measure) and day 3 (as a therapeutic measure). They demonstrated a decreased expression of renal β-catenin associated with a decrease in kidney fibrosis in both the preventive and therapeutic protocols. They showed similar attenuation in renal fibrosis in adriamycin-induced nephropathy (Zhou et al., 2013b). Another group showed that Klotho attenuate kidney fibrosis by blocking Wnt signaling in a UUO model (Satoh et al., 2012). Renal fibrosis is diminished after UUO in mice that overexpress Klotho under the control of the human elongation factor 1α promoter EFmKL46 (Kurosu et al., 2005) in which both canonical and non-canonical Wnt signaling is reduced (Satoh et al., 2012).

Conclusion

Wnt signaling plays important roles in kidney tubules and interstitium after injury. In general, transient Wnt activation in tubules appears to promote healing, whereas persistent Wnt pathway activation in the interstium appears to favor fibrosis. Understanding the divergent effects of the Wnt pathway in these two compartments represents a major challenge (Fig. 3). Ultimately, efforts to develop therapies for acute and chronic injury will require a better understanding of the basic biology of the Wnt pathway in these settings. Given the variety of ways that the Wnt pathway can be

targeted therapeutically, there is reason for optimism that Wnt-directed therapies will ultimately make it to the clinic for patients with kidney disease.

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