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Activation of Canonical Wnt Signaling Meets with Podocytopathy

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WNT signaling regulates a variety of cell fate decisions and developmental processes in species ranging from flies and worms to humans.1 Altered function of the WNT/β-catenin pathway occurs in a diverse array of human diseases, highlighting a crucial role for canonical WNT signaling in the regulation of cellular homeostasis, organ function, and control of tissue patterning during vertebrate embryogenesis. WNTs encompass a family of 19 secreted glycoproteins, short-range signaling molecules activating canonical (β-catenin dependent) and noncanonical (β-catenin independent) intracellular signaling cascades through alternate binding to Frizzled and LDL receptor–related protein 5 and 6 transmembrane receptors.2 WNT signals control levels of cytosolic β-catenin by inhibiting glycogen synthase kinase 3β. Nuclear translocation of activated β-catenin results in interaction with a number of negatively charged ligands including the leukemia and the T cell factor transcription factors. In addition to its intracellular signaling function, β-catenin constitutes a central component of adherens junctions through its interaction with cadherins and other cell adhesion molecules.1,3

A role for canonical Wnt signaling in renal development, specifically branching morphogenesis of the ureteric bud, is well established.4-6 Several Wnt components are implicated, including Wnt 44 and Wnt 9b.7 Deletion of β-catenin in renal epithelial progenitors results in failed condensation of metanephric mesenchyme with reduced nephron formation, whereas constitutive activation induces ectopic leukemia and the T cell factor–dependent transcripts.8 In the mature kidney, increasing evidence implicates Wnt-β–catenin signaling in the pathogenesis of renal interstitial fibrosis.9

A connection between canonical Wnt signaling and glomerulopathy has, until now, been far more tenuous, although the β-catenin complex is expressed at the slit diaphragm.10 In addition, activation of integrin-linked kinase occurs in hereditary nephropathy, and unpublished observations in human podocytes identified nuclear translocation of β-catenin together with upregulation of glycogen synthase kinase 3β in association with specific *NPHS1* mutations (A.K. and M. Saleem). Moreover, a functional consequence of integrin-linked kinase activation in puromycin/adriamycin-induced podocyte damage is nuclear translocation of β-catenin.11

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DISCLOSURES

None.

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The study published in this issue of *JASN* by Dai *et al.*12 builds on these initial observations and provides innovative data that corroborate a role for aberrant activation of canonical Wnt signaling in the pathogenesis of glomerulosclerosis and proteinuria. Preliminary findings in adriamycin nephropathy established the pattern of Wnt activation. To test their hypothesis further, the authors focused subsequent functional experiments on the prototype of the group Wnt1, activated *de novo* by adriamycin injury. They demonstrated exacerbation of podocyte damage in adriamycin nephropathy by exogenous Wnt1, alongside rescue through blocking endogenous Wnt signaling using canonical pathway antagonist Dickkopf1. Subsequent experiments established a role for canonical Wnt signaling in glomerular protein leak by verifying that podocyte-specific ablation of β-catenin in mice protects against podocyte injury, whereas activation enhances proteinuria. A mechanistic explanation is partially provided by the observation that Wnt1-mediated induction of Snail, a known transcriptional repressor of nephrin,13 downregulates nephrin in cultured podocytes. Subsequent detection of Wnt-1/β-catenin activation in the podocytes of patients with FSGS and diabetic nephropathy suggests a link between experimental findings and human disease. Nevertheless, because Wnt-1/β-catenin activation was identified only in a circumscribed number of cases, it would be intriguing to examine sections from a wider range of primary glomerulopathy, including minimal-change and hereditary nephropathies, to help ascertain the spectrum and confirm whether activation might contribute to the pathogenesis of glomerular scarring analogous to processes seen within the renal interstitium.9

Increased expression of mRNA encoding canonical WNTs and Fzd5 in podocytes occurs the day after adriamycin injection, whereas the increase in active β-catenin protein is observed 3 days after injection. Both time points precede onset of overt proteinuria, supporting activation of the canonical pathway during an early stage of injury rather than simply consequent to proteinuria. Interestingly, overexpression of exogenous Wnt1 exacerbates proteinuria and foot process effacement in response to adriamycin but does not produce a phenotype in normal podocytes. This protection may result from redundancy between WNT and interrelated pathways, with the functional consequences becoming unmasked only with additional triggers such as adriamycin. In human disease, chemical damage inducing glomerular proteinuria is unlikely, but it is tempting to speculate that the experimental findings in adriamycin nephropathy may represent situations in which WNT pathway activation becomes a key contributory factor to injury in the presence of other disease triggers such as genetic mutations in predisposition genes *CD2AP*14 or *NPHS2* (R229Q).15 In support of a role in progressive podocyte injury, WNT pathway inhibition by Dickkopf1 does not cause podocyte abnormalities *per se* but ameliorates adriamycin-induced podocyte damage and rescues *NPHS1* mRNA expression.

In contrast to the severe phenotype seen after inactivation of β-catenin targeted to ureteric epithelia, which results in renal dysplasia or aplasia,6 podocyte-specific deletion of β-catenin seemed dispensable to developing or mature podocytes because no glomerular phenotype is observed; however, *β-catenin* null mice challenged with adriamycin were protected against injury as compared with wild-type mice, again supporting a role for canonical signaling in podocyte injury. This protective effect is enhanced in outbred backgrounds, supporting the presence of genetic modifiers and/or epigenetic factors able to influence the phenotype.

The authors offer a mechanistic explanation for their data by showing that Wnt/β-catenin activation in podocytes induces Snail and represses nephrin, confirming a previous independent observation that Wnt2 activation induces Snail and transcriptional repression of nephrin.13 Conversely, recent findings in *Xenopus* demonstrating inhibition rather than activation of canonical Wnt signaling results in loss of expression of the *Xenopus* nephrin orthologue *Xnphs1*,16 which indicates an apparent lack of species conservation and may put

into question the biologic significance of observations in adriamycin nephropathy. Conversely, these disparate observations may simply reflect the complexity of the Wnt signaling and potential differences in spatial/temporal inactivation in different models; however, whether canonical Wnt activation in diseased podocytes results from constitutive activation or occurs through reactivation of developmental signaling cascades by pathologic stimuli remains unclear.

Further studies of downstream targets of Wnt/β-catenin in podocytes including the influence of chromatin binding by β-catenin on the regulation of target gene activation, as well as the contribution of other Wnt ligands and pathway components, are now required to unravel how dysregulation of this ancient pathway challenges podocyte function. Canonical Wnt activation may, for example, be initiated through cross-talk with other pathways such as Notch and PAX2, which play a role of early podocyte differentiation. As the authors propose, delineating the exact role of Wnt activation in podocytopathy will undoubtedly aid an exciting quest for new directed anti-proteinuric therapy. Ultimately, there exists the potential for pharmaceutical modulators of the Wnt signaling pathway following small molecule strategies currently being developed for bone and central nervous system diseases as well as cancer, that in the future may also provide novel therapeutic opportunities to arrest podocyte damage and potentially enhance repair.

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