Notch Signaling: A Common Pathway of Injury in Podocytopathies?

Laura Barisoni
New York University School of Medicine, Department of Pathology and Department of Medicine, Division of Nephrology, New York, New York

doi: 10.1681/ASN.2008040351

The Notch signaling pathway comprises a family of transmembrane receptors, ligands, negative and positive modifiers, and transcription factors with regulatory activity in multiple cellular processes, including cell fate determination, development, differentiation, proliferation, apoptosis, and regeneration. A critical step in the activation of the Notch receptor is proteolytic cleavage of its intracellular domain (NOTCH-IC) by γ-secretase, with consequent translocation into the nucleus and binding to the transcriptional repressor RBPJκ. Notch signaling controls differentiation in multiple organs and is crucial in early podocyte development (during the S-shape body stage), also mediated by γ-secretase activity; however, Notch signaling is not required in later stages of development (capillary loop stage), and its reduced expression coincides with maturation. Thus, notch signaling is essential for initiating differentiation in podocyte progenitors, but its suppression may be necessary for terminal differentiation. Deletion of the gene encoding Notch 2 also results in a kidney phenotype lacking glomeruli and proximal tubules.

More recently, the role of Notch signaling has been investigated in renal diseases. Although this editorial focuses on the study by Waters et al. published in this issue of JASN, it is intriguing to include in the discussion a similar study, conducted virtually simultaneously and that just appeared in the March issue of Nature Medicine. The avenues taken by the two groups are partially different, but both contribute to understanding the role of Notch signaling pathways in the development of podocyte injury and sclerosis. Niranjjan et al. demonstrated increased Notch activity by quantitative reverse transcriptase–PCR analysis of Notch 1 pathway genes and by immunohistochemistry in human and murine diabetic nephropathy and FSGS. Moreover, these authors found that conditional re-expression of NOTCH-IC in mature podocytes at 4 wk of age induced proteinuria and glomerulosclerosis. In vitro experiments revealed that active Notch expression induced apoptosis, a known mechanism resulting in podocytopenia and implicated in glomerular damage in both FSGS and diabetic nephropathy. The article published in this issue by Waters et al. uses a slightly different approach and further contributes to understanding mechanisms, pathways, and resulting phenotypes of ectopic Notch signaling activity. Here, the effect of Notch activation was investigated using a tissuespecific, CRE-loxP–mediated approach to express NOTCH-IC ectopically in embryonic podocytes (at the capillary loop stage). CRE-dependent NOTCH-IC expression in podocyte nuclei coincides with early onset of proteinuria and progressive glomerulosclerosis with increased mesangial matrix and reduction of the capillary diameter (diffuse mesangial sclerosis [DMS]). Both studies show downregulation of differentiated podocyte markers, including nephrin and podocin; however, in distinction from the first study, apoptosis here was not detected. To the contrary, RBPJκ-dependent Notch activation induced cell-cycle re-entry, loss of mature podocyte features, and slit diaphragm architecture.

One question to ask is how activation of the same signaling pathway results in diametrically opposed outcomes: Death versus proliferation. The conclusions of the two previously mentioned studies on the role of Notch activation in glomerular disease are not contradictory, as it may seem, but rather supportive and in line with previous observations. Podocytes reacting to injurious stimuli can follow various pathways that result not only in different phenotypes but also in different glomerular morphology. Glomerular diseases in which podocyte injury seems to be the primary cause have been recently reorganized in a taxonomy of the podocytopathies. This taxonomy is based on etiology and histopathology defined by pattern of glomerular injury and number of podocytes. Injured podocytes may undergo foot process effacement or detach and engage apoptotic pathways, which, according to the podocyte deletion hypothesis, leads to FSGS. Injured podocytes that do not undergo death but rather defective differentiation may produce either collapse of the capillary walls and pseudocrescent formation (collapsing glomerulopathy) when proliferative activity and dedifferentiation are severe, or DMS when low proliferative activity and arrested differentiation are present. Accordingly, in the study conducted by Niranjjan et al., activation of Notch leads to apoptosis, resulting in cell depletion and segmental sclerosis, as expected. The process is mediated by co-activation of the TGF-β1 pathway through engagement of the Notch ligand Jagged 1. In the study by Waters et al., RBPJκ-dependent Notch activation results in an altered state of podocyte differentiation with proliferative activity and DMS. A similar paradigm is not new to the literature. Other examples of phenotypic heterogeneity resulting from a genetic defect in the same protein include nephrotic syndrome secondary to mutations in PLCε1 encoding phospholipase C ε1, whereby a truncating mutation results in early onset of the disease and DMS, whereas a nontruncating mutation results in a later onset of the disease manifesting as FSGS; coenzyme Q2 nephropathy, whereby mitochondrial
dysfunction results either in podocytopenia and FSGS or in increased proliferative activity and collapsing glomerulopathy, and mutations in the nuclear transcription factor WT1 producing DMS (Denys-Drash syndrome) or in FSGS (Frasier syndrome).

The specific mechanism by which activation of the Notch signaling pathway in podocytes results in activation of apoptotic stimuli or abnormal differentiation and proliferation still needs elucidation. As suggested by Waters et al., Notch activation may represent a common pathway to podocyte injury. The resulting phenotype and glomerular histopathology may depend on levels of Notch signaling in podocytes or the activation of collateral pathways, which may positively or negatively influence Notch signaling. Notch signaling is also mediated by mitochondria functionality, a known modulator of apoptosis and proliferation. Given the role of Notch during different stages of development, it is reasonable to speculate that various forms of glomerular injury are time dependent. Last, the microenvironment and genetic background should also be considered as potential modulators on the level of Notch signaling, as demonstrated in other organ systems.

On the basis of these recent observations, it would be helpful to investigate the role of Notch signaling in other podocytopathies, because it may represent a common pathway for podocyte injury and a potential candidate for new therapeutic strategies.

**REFERENCES**


**DISCLOSURES**

None.

**Dialysis Dosage in Acute Kidney Injury: Still a Conundrum?**

Ravindra L. Mehta and Jose´e Bouchard
Division of Nephrology, Department of Medicine, University of California San Diego, San Diego, California

In medicine, a key necessity is understanding how to dose therapy to achieve a desired response. For treatment of patients with chronic and acute kidney problems, dialysis techniques are routinely applied; however, establishing a dosage–response relationship for dialysis techniques is challenging both in the chronic and the acute setting. In this issue, Tolwani et al. report the results of a single-center, randomized, controlled trial comparing a high dosage (35 ml/kg per h) with a standard dosage (20 ml/kg per h) of continuous venovenous hemodiafiltration in patients with severe acute kidney injury (AKI). There was no benefit for renal recovery or overall survival with the higher dosage. These results are contrary to three other controlled trials published recently. These studies showed a survival advantage by providing a higher dosage of dialysis, either with a continuous renal replacement therapy dosage ≥35 ml/kg per h or with daily compared with every-other-day intermittent hemodialysis. Only one other study failed to show a survival benefit despite application of higher dosages; however, it was underpowered. Given the varied results of these studies, several important questions emerge. Is dialysis...