The Promise of Well-Being: Stay in Shape with N(i)ck

Thomas Benzing

Department of Medicine, Centre for Molecular Medicine, and Co-llege Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany


doi: 10.1681/ASN.2009040453

Just more than a decade ago, a report of a rare human genetic disorder initiated a new spurt of research that profoundly changed our understanding of the glomerular filtration barrier. In that landmark article,1 mutations in the gene encoding nephrin identified the cause of congenital nephrotic syndrome of the Finnish type. Subsequent studies expanded our understanding of glomerular filtration barrier function and disease progression. For the first time, researchers realized the complexity of the glomerular filtration barrier and appreciated the multiple steps involved in the filtration process, including the role of nephrin in maintaining slit diaphragm integrity, providing structural support, and coordinating dynamic interactions with parajunctional complexes.

The Promise of Well-Being: Stay in Shape with N(i)ck

Thomas Benzing

Department of Medicine, Centre for Molecular Medicine, and Co-locne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany


doi: 10.1681/ASN.2009040453

Just more than a decade ago, a report of a rare human genetic disorder initiated a new spurt of research that profoundly changed our understanding of the glomerular filtration barrier. In that landmark article,1 mutations in the gene encoding nephrin identified the cause of congenital nephrotic syndrome of the Finnish type. Subsequent studies expanded our understanding of glomerular filtration barrier function and disease progression. For the first time, researchers realized the complexity of the glomerular filtration barrier and appreciated the multiple steps involved in the filtration process, including the role of nephrin in maintaining slit diaphragm integrity, providing structural support, and coordinating dynamic interactions with parajunctional complexes.
cell junction that connects neighboring podocytes, the visceral epithelial cells of the glomerulus. These neighboring podocytes elaborate long, regularly spaced, interdigitated foot processes that enwrap the glomerular capillaries and form a 40-nm-wide filtration slit bridged by the slit diaphragm.

Further studies suggested that nephrin and associated proteins, in addition to their role as structural components of the slit diaphragm, act as signaling molecules to control podocyte development, cytoskeletal architecture, cell shape and viability, and the function of the glomerular filtration barrier. Much insight into the signaling function of the slit diaphragm protein complex resulted from the identification of nephrin-interacting proteins. Yet the mechanisms that control ultrastructure and shape of the highly organized podocyte foot process remain poorly understood. This changed with the finding that nephrin binds Src homology 2 (SH2)/SH3 domain-containing Nck adaptor proteins, which in turn seems to control the podocyte cytoskeleton in vivo. The Nck family of adaptors (mammals carry two related Nck genes, Nck1 and Nck2) functions in coupling phosphotyrosine signals to actin cytoskeletal reorganization. Each of these proteins contains multiple protein interaction domains: three SH3 domains that are known to interact with proline-rich binding partners such as the actin organizers WASP, SPIN90, and dynamin and an SH2 domain that mediates binding of transmembrane receptors and adhesion proteins through phosphotyrosine-dependent protein interactions. Nephrin ectodomains recruit the Src family tyrosine kinase Fyn to phosphorylate the nephrin cytoplasmic tail, allowing recruitment of Nck and inducing localized Nck-driven actin polymerization. Notably, selective gene deletion of Nck1 and Nck2 from podocytes in transgenic mice results in severe defects in the formation of podocyte processes and in congenital nephrotic syndrome. Although the profound changes in cell shape and podocyte morphology in this model mirror the stereotypical reaction of podocytes to injury or damage, the phenotype is clearly a developmental defect—mice are born without Nck1 or Nck2 in podocytes—and does not clarify the role of nephrin-Nck signaling. Although Jones et al. clearly demonstrate, nephrin phosphorylation is maintained in the adult glomerulus supporting the importance of signaling at the slit diaphragm for regulation of podocyte cell shape, cytoskeletal architecture, and cell viability.

It is worth noting that these new findings have the same limitations as the original report concerning a developmental role of nephrin-Nck signaling. Although Jones et al. clearly demonstrate that Nck1 and Nck2 are essential for developing and maintaining the complex ultrastructure of podocyte secondary processes, both articles lack direct proof that Nck proteins exclusively act through the nephrin/slit diaphragm axis in vivo. In fact, this has to be addressed in future studies, for instance using knock-in mouse models of nephrin with mutated tyrosine residues. Despite this limitation, Jones et al. undoubtedly demonstrate the importance of Nck in controlling the ultrastructure of podocyte foot processes in maintaining the integrity of the glomerular filtration barrier.

ACKNOWLEDGMENTS

I thank members of the Benzing laboratory for helpful discussions and critically reading the manuscript.
Glomerular Filtration: Still Sympathetic to Endothelin’s Influence?

Tracy E. Hunley and Valentina Kon

Division of Nephrology, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee

doi: 10.1681/ASN.2009050503

Methodologic and analytic advances in molecular genetics identify many disease-predisposing variants in the human genome. One of the challenges presented by these studies is to define the mechanisms by which a given genetic variant affects a pathophysiologic disorder. This inevitable quandary confronts the study of Chen et al.1 in this issue of JASN. The authors previously reported that a genetic polymorphism of chromogranin A (CHGA), a soluble protein released from secretory granules of chromaffin cells and sympathetic nerves, predicts hypertensive ESRD in black patients. Using population genetic techniques, they further showed that the CHGA locus is a trans-QTL for endothelin-1 secretion and that CHGA stimulates endothelin release from endothelial cells. In view of the major role for endothelin postulated in the pathogenesis of a variety of cardiovascular and renal diseases, the authors questioned whether endothelin secretion is the mechanistic link between CHGA and renal dysfunction.

Using cultured human umbilical vein endothelial cells, Chen et al.1 now show that CHGA increases release of endothelin along with other peptides typically stored in Weibel-Palade bodies, including von Willebrand factor and angiopoietin 2. CHGA also increases endothelin secretion from mouse glomerular endothelial cells, and co-culture of CHGA-exposed glomerular endothelial cells with mesangial cells potentiates pericyte-driven secretion of growth factors, thereby stimulating secretion of growth factors, which in turn regulate the level of endothelin secretion. Thus, CHGA increases endothelin secretion from mouse glomerular endothelial cells, and co-culture of CHGA-exposed glomerular endothelial cells with mesangial cells potentiates secretion of GFR-1.

In humans, plasma CHGA correlates positively with plasma endothelin and negatively with GFR. A promoter haplotype for CHGA predicts the level of GFR in individuals with GFRs in the normal range, whereas CHGA haplotypes in the 3′ untranslated region associate with GFR in individuals with progressive renal disease. The conclusion that CHGA triggers exocytotic release of endothelin from the glomerular endothelium and that this, in turn, regulates the level of GFR in normal and declining renal function offers some novel implications. These include genetic modulation of GFR in normal and diseased kidneys under the potential influence of the sympathochromaffin protein, the utility of circulating

---

See related article, “Nck Proteins Maintain the Adult Glomerular Filtration Barrier,” on pages 1533–1543.