Pediatric Nephrotic Syndrome: From the Simple to the Complex

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Summary: Remarkable advances have been made in the past decade in understanding the pathophysiology of idiopathic nephrotic syndrome. Although the initiating events leading to the onset of proteinuria still are not well defined, it has become increasingly clear that many glomerular diseases can be classified as podocytopathies, with injury to the podocyte playing a major role in the development and progression of disease. A complex interaction of immune system mediators, slit diaphragm signal transduction, podocyte injury and conformational change, and mediators of apoptosis and fibrosis determine the extent and nature of proteinuria and progression of glomerulosclerosis. New insights into the pathogenesis of idiopathic nephrotic syndrome likely will lead to innovative therapies and new approaches to management and prevention.

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In the 10 years since the first version[1] of this article, there has been remarkable progress in the understanding of the pathophysiology of idiopathic nephrotic syndrome (INS). In particular, elucidation of the genetic causes of congenital NS and familial focal segmental glomerulosclerosis (FSGS), as well as new insights regarding podocyte biology, have led to novel ways of thinking about NS, its pathogenesis, and, perhaps most importantly, its management and treatment. An ever-evolving and increasingly complex web of pathways involved in the development of INS and progression of glomerulosclerosis continues to be investigated. The purpose of this article is to present these new understandings of the pathophysiology of INS, in particular with regards to FSGS and minimal change nephrotic syndrome (MCNS).

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PODOCYTE BIOLOGY AND GENETIC MECHANISMS OF NS

Nephrin and the Slit Diaphragm

Perhaps the most exciting development in recent years in understanding the pathophysiology of NS has occurred in the area of podocyte biology and the structure of the slit diaphragm (SD). The glomerular filtration barrier consists of the fenestrated capillary endothelium, the extracellular basement membrane, and the intercalated podocyte foot processes, connected by 35- to 45-nm slit diaphragms. NS is associated with the biopsy finding of effacement of podocyte foot processes. Effacement is characterized by flattening of the podocyte, retraction of foot processes, and reduction in the number of SDs.[2] This effacement of the podocytes long was thought to be a secondary phenomenon of NS. Recent thinking, however, has shifted toward the podocyte as playing a primary role in the development of proteinuria and progression of glomerulosclerosis. It is now clear that, far from being a simple passive filter, the numerous components of the SD act as a complex signaling platform and play an important role in podocyte function. Similarly, it increasingly is being recognized that MCNS and FSGS can be

classified as podocytopathies, in which disruption of SD and normal podocyte function can lead to proteinuria and glomerular disease.

A breakthrough in the understanding of podocytes and the SD came in 1998 with the discovery of nephrin and its associated gene, *NPHS1*, while investigating the genetic cause of Finnish-type congenital nephrotic syndrome (FNS). FNS is an autosomal-recessive disease characterized by development in the neonatal period of massive proteinuria, edema, and eventual end-stage kidney failure. FNS is caused by mutations in the NPHS1 gene on chromosome 19. The protein product of *NPHS1* is nephrin.[3] Mutations in *NPHS1* lead to absence of nephrin in the SD, disrupting this component of the glomerular filtration barrier and leading to proteinuria. Although more than 70 mutations in *NPHS1* have been identified with FNS, a few also have been found that are associated with a milder form of FNS as well as with FSGS.[4]

Nephrin is a transmembrane protein with a short intracellular and long extracellular domain. Nephrin molecules interact with each other across the space between podocyte foot processes, joining to form a zipper-like structure with pores on either side of the center seam and thereby forming the filtering structure of the SD. Besides forming the skeleton of the SD filter, nephrin also acts as a signal transducer. The intracellular portion of nephrin can be phosphorylated, which, in turn, leads to changes in interaction with the podocyte actin cytoskeleton, inducing conformational changes in the podocyte that may play a role in proteinuric diseases.[5]

Investigations regarding familial forms of FSGS have led to the discovery of other key components of the SD. Mutations in the *NPHS2* gene on chromosome 1 are the cause of a familial, autosomal-recessive form of FSGS. The protein product of *NPHS2* is podocin, another component of the SD. Mutations in α-actinin-4, encoded by the gene *ACTN4* on chromosome 19, and mutations in *TRPC6* on chromosome 11, are associated with autosomal-dominant forms of FSGS. Podocin, α-actinin-4, and TRPC6 all are podocyte proteins essential to the functioning of the SD and maintenance of the filtration barrier to protein loss.[4] Heterozygous mutations in the protein CD2AP have been found in 2 patients with primary FSGS,[6] and, more recently, a homozygous mutation in this protein has been implicated in a patient with FSGS (although the parents had heterozygous mutations and no proteinuria).[7] CD2AP interacts with nephrin and appears to be involved in anchoring nephrin to the actin cytoskeleton of the podocyte.[5]

The SD, Podocyte Proteins, and Signal Transduction

A growing number of SD proteins continue to be found and their role in the complex signaling pathways of the podocyte elucidated in normal and proteinuric states. Indeed, signal transduction through the SD appears to play a critical role in regulating the podocyte cell cycle, polarity, cytoskeleton, and apoptosis.[8] It is beyond the scope of this review to present in depth the multiplicity of signaling pathways in the podocyte and SD and their complex interactions (the reader is referred to several excellent recent reviews on the subject).[2,9,10] However, a few of these pathways are described in the following paragraphs.

During formation of the SDs, the interaction of the extracellular domains of nephrin leads to transient activation of Fyn, a member of the Src tyrosine kinase family. Activation of Fyn, in turn, leads to phosphorylation of tyrosine residues in the intracellular tail of nephrin. Phosphorylation of nephrin leads to recruitment of the adaptor proteins Nck 1 and 2, which induce actin polymerization and stabilization of the SD complex by attachment to the podocyte cytoskeleton. After SD formation is complete, nephrin is dephosphorylated and anchored to the actin cytoskeleton through CD2AP and podocin. During podocyte injury, the podocyte cytoskeleton and SD framework is disrupted, leading to podocyte foot process effacement and proteinuria. During the healing phase, nephrin molecules again interact to form the SD framework and become phosphorylated, thereby recruiting Nck 1 and 2 and inducing regeneration of actin filaments and restoration of normal podocyte architecture.[5]

Phosphorylation of nephrin also leads to activation of phosphoinositide 3-OH kinase