Invited Lecture

Is nephrin biogenesis a therapeutic target of immunosuppressants on the proteinuria ?

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Remission of proteinuria in the idiopathic nephrotic syndrome (NS) can be induced by glucocorticoids with or without immunosuppressive agents; however, the therapeutic mechanism of these drugs for antiproteinuric effect remained largely unknown. The pathomechanism of proteinuria in NS is not completely understood but recent characterization of nephrin opened new avenues for research. Besides its central role in the development of congenital NS, nephrin has been implicated in the pathogenesis of acquired forms of NS. Nephrin is a transmembrane glycoprotein of the immunoglobulin superfamily and, like other glycoproteins, nephrin biogenesis involves steps such as synthesis, folding, modifications, including N-glycosylation, and targeting to the plasma membrane. Endoplasmic reticulum (ER) is the site of modifications that lead protein folding. Under certain pathological conditions, the influx of unfolded proteins exceeds the folding/processing capacity of the ER. This ER imbalance, termed ER stress triggers signaling pathways to return the ER to its physiological state.

In this talk, first I present the possible evidence being able to show the direct action of glococorticoid and mizoribine against the glomerular podocyte. Second I review the currently known mechanism of quality control system in the ER at both normal and pathological condition. Third I discuss that the ATP depletion due to glucose starvation and hypoxia for podocyte leads to alteration of nephrin biogenesis with its intracellular trafficking. Finally glucocorticoid, mizoribine, and cyclosporin A rescue this alteration of nephrin biogenesis through affecting the different sites involved in maintaining of intracellular energy balance of podocyte.