The Changes of Podocyte and Slit Diaphragm in Proteinuric Conditions

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The clarification of the pathogenic mechanism of proteinuria is one of the most important themes in the nephrology field. Although the role of the glomerular basement membrane as a barrier of the glomerular capillary wall has been emphasized in the past three decades, it is becoming clear that podocyte also plays a critical role as a barrier. Podocyte is a highly specialized terminally differentiated cell characterized by the interdigitating foot processes and the slit diaphragm (SD) connecting the adjacent foot processes. Some recent studies revealed that the SD functions as a final permeability barrier of the glomerular capillary wall and that the dysfunction of the SD is involved in the development of proteinuria in several glomerular diseases such as minimal change type nephrotic syndrome (MCNS) and membranous nephropathy. We and other group have previously reported that nephrin and podocin are localized at the SD and that their expressions are clearly altered already at the early phase of puromycin aminonucleoside nephropathy, an experimental model of MCNS[1,3]. These findings indicate that these molecules are critical components of the SD, and that the alteration of their expression is involved in the development of proteinuria. We have also reported that the SD injury is involved in the development of mesangial proliferative glomerulonephritis[4]. Recently, we precisely analyzed the expression of the SD molecules, nephrin, podocin and CD2AP in passive- and active-Heymann nephropathy which are widely used as experimental models of membranous nephropathy[5]. Immunohistochemical and polymerase chain reaction (PCR) studies clearly showed that the expression of both nephrin and podocin already decreases at the early phase of the disease, prior to the observation of proteinuria. We detected urinary nephrin on day 7 of the disease, when abnormal proteinuria had not yet been detected. Dual-labeling immunohistochemistry and Western blot analysis with sequential extracts of glomeruli clearly showed that nephrin dissociates from podocin in the proteinuric state. These findings suggest that the alteration in the interaction of the SD components, as well as the decrease in their expression contributes to the development of proteinuria in membranous nephropathy.

In my presentation at the meeting, I will show our studies on the expression of the SD associated molecules in several experimental models of glomerular disease and also show that in clinical cases showing severe proteinuria.

References

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