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Integrating Tissue Proteomics and Urinary Analyses to Capture Dynamic Podocyte Injury

To the Editor: We congratulate Fervenza *et al.*[1] for their comprehensive and elegant proteomic analysis of podocyte proteins across minimal change disease, primary and secondary focal segmental glomerulosclerosis, and membranous nephropathy (MN). By applying tissue-based proteomics to carefully phenotyped cohorts, the authors provide important insights into disease-specific patterns of podocyte protein expression. Notably, they report a marked reduction of slit diaphragm and cytoskeletal podocyte proteins in minimal change disease and focal segmental glomerulosclerosis, whereas such reduction was not observed in MN; a finding they appropriately describe as surprising, supporting that the pathophysiology of podocyte injury in MN differs from that in minimal change disease and focal segmental glomerulosclerosis.

Recent mechanistic evidence by Lahme *et al.*[2] indicates that in MN, immune complex clearance on the podocyte surface is achieved through vesicle-mediated extrusion into the urinary space, resulting in loss of podocyte membrane components and structural proteins, including nephrin, podocin, and α-actinin-4, the same proteins reported as preserved at the tissue level by Fervenza *et al.*[1] In contrast, non-MN extracellular vesicles show a low abundance of podocyte proteins.[2]

However, if interpreted together, these mechanistic data and the tissue-based proteomic findings may suggest that differences between MN and other podocytopathies may reflect not only distinct mechanisms, but also different dynamics of podocyte injury. Therefore, rather than contradicting the conclusions by Fervenza *et al.*,[1] recent evidence may suggest how dynamic vesicle-mediated redistribution of podocyte proteins in podocytopathies could lead to a distinct tissue proteomic signature.[3]

Indeed, tissue-based proteomics provides a highly informative but inherently static snapshot of podocyte protein abundance. This approach may therefore not fully capture ongoing and spatially heterogeneous processes of podocyte protein loss,[4] particularly when proteins are dynamically redistributed or shed into the urinary compartment through vesicle-mediated pathways. In this context, apparent preservation at the tissue level does not necessarily exclude active protein loss, but rather highlights the need to integrate static tissue-based measurements with dynamic urinary analyses to obtain a more complete picture of podocyte injury.

From a clinical and translational perspective, complementary analyses of podocyte proteins in tissue and urine may therefore offer a more complete and dynamic assessment of podocyte injury. Integrating tissue-based measurements with urinary analyses could improve interpretation of disease mechanisms and help refine our understanding of distinct clinical entities converging on the podocyte.

DISCLOSURE

All the authors declared no competing interests.

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