

Multi-modal microscopy to identify MAGI2 α as the crucial isoform in podocyte differentiation in mouse kidneys

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MAGI2 is a membrane associated guanylate kinase localized to the base of the slit diaphragm where the renal filtration takes place. The slit diaphragm is a multiprotein complex that connects adjacent kidney's specialized epithelial cells, the podocytes, via pairing nephrin molecules that are anchored in the cell membrane of the opposing foot processes. Nephrin interacts with several protein including MAGI2. This gene is under the control of the Wilms'tumor suppressor WT1 that plays key functions in kidney development.

To clarify result discrepancies on the role of Magi2 isoforms for podocyte function, we analyzed kidneys from Magi2 knockout mice lacking only one isoform, Magi2 α , the predominant isoform produced in glomerular podocytes.

Scanning electron microscopy revealed morphological changes of footprocesses in mutant podocytes that displayed poorly organized extensions reminiscent of filopodia compared to wild type phenotype presenting sophisticated interdigitations.

In addition, Transmission electron microscopy (TEM) showed defects in cytoskeletal organization and lack of slit diaphragms.

Light microscopy revealed an alteration of the nephrin immunostaining suggesting an altered cellular localization proved by immunogold labelings observed by TEM.

Thanks to these four microscopic approaches, we conclude that MAGI2 is required for proper localization of nephrin within footprocesses and thus the assembly of the slit diaphragm. Additional results indicate that the loss of MAGI2 expression correlates with glomerular diseases in mouse and humans.