MAGI-2 plays a crucial role in homeostasis of the slit diaphragm in kidney podocytes

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[Introduction] Podocytes surround the apical aspect of the glomerular basement membrane and form the final barrier to plasma proteins. In particular, the slit diaphragms (SDs), which ordinarily are observed as gaps between foot-processes, play a crucial role in the filtering system. Membrane-associated guanylate kinase inverted 2 (MAGI-2) is a component of the slit diaphragm (SD) of podocytes. We previously reported that MAGI-2 whole knockout (KO) mice exhibit a complete disappearance of SD and die within 24 hours after birth because of anuria. However, podocyte-specific functions of MAGI-2 in adult mice remain unknown because of the neonatal lethality in KO mice.

[Methods] We generated podocyte-specific MAGI-2 KO (MAGI-2pdKO) mice and performed phenotypic analyses in adulthood. Moreover, we analyzed the interaction between MAGI-2 and other SD molecules using cultured podocytes and biochemical techniques.

[Results] MAGI-2pdKO mice exhibited massive albuminuria, which resulted in glomerulosclerosis, and died within 5 months of age because of renal failure. Loss of MAGI-2 in podocytes induced nuclear translocation of dendrin, which is also a component of the SD complex. Dendrin translocates from the SD to the nucleus of injured podocytes, promoting apoptosis. Indeed, MAGI-2pdKO mice resulted in podocyte apoptosis leading to podocyte loss. Moreover, podocytes from MAGI-2pdKO mice exhibited a cytoplasmic localization of nephrin (major component of SD complex), SD disruption, and foot-process effacement. Additional experiments using cultured podocytes overexpressing both MAGI-2 and nephrin showed that these proteins colocalized at the cell-cell contacts. Furthermore, we found that MAGI-2 interacts with nephrin in vitro.

[Conclusion] Therefore, we demonstrated that MAGI-2 determines the localization of dendrin and nephrin at the SD into foot-processes. We also demonstrated that the abnormal localization of nephrin and dendrin by MAGI-2 disappearance is a cause of podocyte injury. In summary, MAGI-2 plays a critical role in SD homeostasis in mature podocytes.