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Commentary

The sponging effect of a lncRNA on a miRNA contributes to diabetic nephropathy

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Vertebrate kidneys play a vital role in draining harmful metabolic waste products in urine, in addition to maintaining homeostasis. Kidneys are composed of a charge- and size-selective glomerular filtration barrier (GFB) that facilitates the excretion of small molecules and retains proteins and other macromolecules in the blood. The permselective GFB comprises three layers: endothelial cells, a basement membrane, and podocytes. Podocytes are highly specialized visceral epithelial cells, which provide coverage to the glomerular capillaries and supply growth factors for endothelium and matrix components to the basement membrane. Podocytes develop unique cytoplasmic extensions known as the foot processes. A specialized gap junction between adjacent interdigitating foot processes, known as the slit diaphragm, forms the major size-selective filtration barrier to prevent protein leakage. Studies suggest that podocytes are instrumental for the integrity of GFB and almost represent the kidney's filtration function.[1]

By virtue of their function, podocytes are constantly exposed to hemodynamic changes and metabolic fluctuations and are prone to an array of insults. Impaired renal function resulting from podocyte injury and dysfunction is central to the pathophysiology of proteinuric glomerular diseases, including diabetic nephropathy. Podocytes are post-mitotic and quiescent (arrested at G0 phase of the cell cycle); unlike other glomerular cells (endothelial and mesangial cells), they typically do not proliferate.[2] Although terminal differentiation of podocytes is achieved with permanent withdrawal from the cell cycle, these cells express a wide range of cell cycle proteins. Forced re-entry of terminally differentiated podocytes into the cell cycle by various means, including overexpression of cyclinD1, cyclin-dependent kinase 4/6, and induction of Notch signaling, results in mitotic maladaptation, which leads to aneuploidy, multiple/irregularly shaped nuclei, and failure of cytokinesis. Mitotic maladaptation of terminally differentiated cells (neurons, cardiomyocytes, and podocytes) by forced cell cycle re-entry results in cell death in a process known as mitotic catastrophe (MC).[3] Diabetic nephropathy, a leading cause of end-stage renal disease, is characterized by abnormal mitosis and fewer podocytes. MC was observed in podocytes examined in diabetic urine and kidney biopsy specimens from diabetic patients.[4] Although it is known that forced re-entry of podocytes to the cell cycle causes MC and podocyte loss in diabetic kidney disease due to MC, the specific stimuli and mechanism that provoke MC of podocytes in diabetic settings are unknown.

In this issue of *Molecular Therapy: Nucleic Acids*, the study by Wang et al.[5] contributes to our understanding of how podocytes undergo MC under the influence of the intergenic long non-coding RNA (lncRNA) MIAT. Elevated MIAT levels were observed in podocytes exposed to high glucose (30 mM) *in vitro* and a streptozotocin-induced diabetic mouse model *in vivo*. Elevated MIAT levels in plasma from diabetic nephropathy patients were associated with impaired kidney function. The study by Wang et al.[5] suggests a significant association of MIAT with podocyte injury in high-glucose conditions, as evidenced by decreased expression of putative podocyte markers such as podocin, synaptopodin, and ZO-1. Ectopic expression of MIAT distorted the podocyte cytoskeleton, while ablation of MIAT expression partially preserved F-actin rearrangement. It is noteworthy that the integrity of the cytoskeleton is crucial for the stable attachment of podocytes to the basement membrane. Diabetic mice show aberrations in all three components of GFB, including effacement of the podocyte foot process, thickening of the basement membrane, and expansion of endothelial cells. On the other hand, mice in which MIAT was knocked out were protected from podocyte injury, accompanied by improved kidney function, as evidenced by decreased proteinuria.

Furthermore, the study by Wang et al.[5] revealed that podocytes either exposed to high glucose or ectopically expressing MIAT show increased expression of Sox4, and features of MC such as collapse of mitotic spindles, and cell-cycle arrest at the G2/M stage. Overexpression of Sox4 causes cell cycle re-entry of otherwise quiescent podocytes via inducing p53 and its target p21. Sox4 interacts with p53, thus preventing its ubiquitination by Mdm2 and fostering its acetylation by recruiting CBP/p300 (Figure 1). Using a computational approach, Wang et al.[5] found that miR-130b-3p could bind MIAT and the 3′ UTR of Sox4. The investigators observed reduced miR-130b-3p levels (unlike MIAT levels) in plasma from patients with diabetic nephropathy. The significant finding of this study is that MIAT sponges and thus prevents miR-130b-3p from suppressing Sox4 mRNA levels in podocytes (Figure 1). The sponging effect of MIAT on miR-130b-3p is the molecular basis for elevated levels of Sox4 and resultant cell cycle re-entry, mitotic failure, and associated cell death or detachment of podocytes. Administration of mice with miR-130b-3p antagomir elicited Sox4 levels *in vivo*. Depletion of miR-130b-3p levels by antagomir manifested in foot process effacement and proteinuria.

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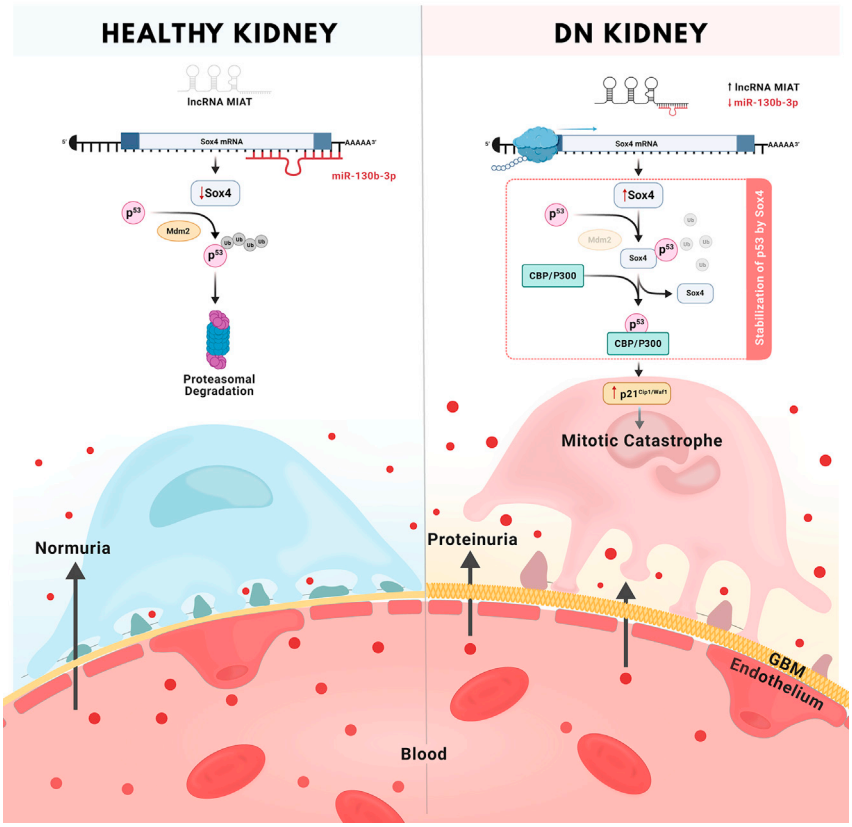

Figure 1. Mechanism of lncRNA MIAT-induced mitotic catastrophe of podocytes and implications in diabetic nephropathy (DN)

Elevated lncRNA MIAT in podocytes under diabetic settings sponges miR-130b-3p and prevent it from degrading Sox4 mRNA. Accumulation of Sox4 in the diabetic milieu rescues p53 from ubiquitination by Mdm2 and elicits acetylation by CBP/P300. p53 in turn mediates cell-cycle arrest in G2/M stage via expression of the CDK inhibitor p21. In addition to mitotic failure, effacement of the podocyte foot process and thickening of the glomerular basement membrane (GBM) are observed in the diabetic kidney. Podocytes with aneuploidy and multiple nuclei detach or die, impairing glomerular filtration and protein.

Podocytes isolated from mice administered with miR-130b-3p antagomir displayed G2/M arrest and features of MC.

The seminal finding of this study[5] is uncovering the novel function of the lncRNA MIAT, which leads to a sponging effect on miR-130b-3p in the setting of diabetic nephropathy. Unraveling the mechanism by which cell cycle re-entry causes cell death and exploring the factors to combat such cell death in terminally differentiated podocytes produces excellent advances in treating and preventing diabetic nephropathy. This study provides novel molecular insights and a greater understanding of how podocytes in diabetic kidney disease undergo MC. This study is a step toward discovering druggable microRNA (miRNA) (miR-130b-3p) or lncRNA MIAT, which can be used as diagnostic markers as well as for tailored therapeutic approaches for diabetic nephropathy.

REFERENCES

1. Kopp, J.B., Anders, H.J., Susztak, K., Podestà, M.A., Remuzzi, G., Hildebrandt, F., and Romagnani, P. (2020). Podocytopathies. Nat. Rev. Dis. Primers *6*, 68. https://doi.org/10.1038/s41572-020-0196-7.

2. Wu, Y.S., Liang, S., Li, D.Y., Wen, J.H., Tang, J.X., and Liu, H.F. (2021). Cell cycle dysregulation and renal fibrosis. Front. Cell Dev. Biol. *9*, 714320. https://doi.org/10.3389/fcell.2021.714320.

3. Lasagni, L., Lazzeri, E., Shankland, S.J., Anders, H.J., and Romagnani, P. (2013). Podocyte mitosis - a catastrophe. Curr. Mol. Med. *13*, 13–23. https://doi.org/10.2174/1566524011307010013.

4. Hara, M., Oohara, K., Dai, D.F., and Liapis, H. (2019). Mitotic catastrophe causes podocyte loss in the urine of human diabetics. Am. J. Pathol. *189*, 248–257. https://doi.org/10.1016/j.ajpath.2018.10.016.

5. Wang, Z., Chang, Y., Liu, Y., Liu, B., Zhen, J., Li, X., et al. (2022). Inhibition of the lncRNA MIAT prevents podocyte injury and mitotic catastrophe in diabetic nephropathy. Mol. Ther. Nucleic Acids *28*, 136–153. https://doi.org/10.1016/j.omtn.2022.03.001.