Editorial

The emerging landscape of lncRNAs in diabetic nephropathy

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Comment on: Sun SF, Tang PM, Feng M, *et al.* Novel lncRNA Erbb4-IR promotes diabetic kidney injury in db/db mice by Targeting miR-29b. Diabetes 2018;67:731-44.

Submitted Feb 26, 2018. Accepted for publication Feb 27, 2018.
doi: 10.21037/tcr.2018.03.07
View this article at: http://dx.doi.org/10.21037/tcr.2018.03.07

With the acceleration of global aging, the incidence of diabetes mellitus (DM) is significantly increasing and is accompanied by a significant increase in the incidence of diabetic nephropathy (DN), a major complication of diabetes. DN is the leading cause of end-stage renal disease (ESRD) in DM, with a prevalence of 20–40%, and is the major cause of death and disability in DM patients (1). DN is characterized by progressive renal interstitial fibrosis (2), leading to a series of pathological changes, including mesangial expansion and mesangial matrix overproduction, and excessive thickening of tubular basement membranes and extracellular matrix (ECM) accumulation in glomerular (3). Moreover, the progress of DM is involving in various signaling pathways, including the nuclear factor-kappa B pathway (4), Hippo pathway (5), and the transforming growth factor-beta (TGFβ) pathway (6). In the past few decades, the diagnosis and treatment of DN has improved. However, it is still very difficult to distinctly reduce the mortality of this population (7,8). Therefore, an effective treatment to improve the long-term survival of DN patients is urgently needed.

Non-coding RNAs (ncRNAs) include microRNAs (miRNAs) (9), circular RNA (cicrcRNA) (10), and long non-coding RNA (lncRNA) (11). LncRNAs were firstly discovered in eukaryotes. The length of the lncRNA transcript exceeds 200 nucleotides (12). The possible origins of lncRNAs include insertion transposable elements, gene mutations, tandem duplication events, chromatin rearrangement, and retrotransposition (13). Moreover, lncRNAs can be divided into five categories depended on their proximity to the genomes of neighbouring transcripts: intronic synthesis, sense strand synthesis, antisense strand synthesis, intergenic synthesis (lincRNAs), and bidirectional synthesis (14,15). Although lncRNAs do not translate into functional proteins, they act as pivotal regulators in various biological processes mediated by RNA or functional short peptides (16). LncRNAs play a vital role in the occurrence and development of DN, and regulate ECM accumulation to promote renal fibrosis. Thomas *et al.* (17) found that lncRNA ANRIL (also known as CDKN2B-AS1) promotes kidney injury by improving the expression of fibronectin (FN) and type IV collagen (Col1α4). Zhang *et al.* (18) revealed that plasmacytoma variant translocation 1 (PVT1) is closely associated with TGF-β and c-myc expression, that the overexpression of PVT1 is accompanied by increases in TGF-β and c-myc expression, and that PVT1 overexpression enhances ECM accumulation. Interestingly, an RNA sequencing study revealed details of the lncRNA gene transcriptome and the dynamic and time-dependent function of proximal tubular cells in mice (19). The findings should inform lncRNA-based diagnosis and therapies for DN.

A recently published article in *Diabetes* by Sun *et al.* (20) has provided a novel insight about the relationship between Smad3-dependent lncRNA Erbb4-IR and type-2 DN (T2DN) in db/db mice. In this study, the authors identified

that Erbb4-IR is markedly upregulated in T2DN induced by advanced glycation end product rather than high glucose via a Smad3-dependent mechanism, because deletion of Smad3 but not Smad2 was blocked. Furthermore, they used kidney-specific silencing of Erbb4-IR of db/db mice to study the function of Erbb4-IR in DN, and demonstrated the markedly increased expression of miR-29b by the silencing of Erbb4-IR *in vivo* and *in vitro*. The collective results of the study revealed that Erbb4-IR promotes renal fibrosis in T2DN by suppressing miR-29b, and that the Erbb4-IR-miR-29b axis is a key mechanism in kidney injury during the progression of DN. These findings may provide a novel therapy for T2DN. However, I have three issues concerning this article. First, the authors reported that the db/m or db/db mice were treated at 12, 15, and 18 weeks of age with the vector containing shRNA sequence targeting Erbb4-IR (Erbb4-IR-shRNA-pSuper.puro), and were sacrificed at week 20. I am not sure that whether the effect of shRNA vector in, *in vivo* experiments can be maintained for two months. A protracted lncRNA silencing is usually achieved by constructing lentivirus stably silenced cell lines or crispr/cas9 knockout cell lines *in vivo*. Secondly, miRNAs genes are first transcribed into polyadenylated primary transcripts (pri-miRNAs), which are cleaved by the Drosha ribonuclease III enzyme to produce an approximately 70-nt stem-loop precursor miRNA (pre-miRNA), At this point, pre-miRNA does not have a 3'UTR. Therefore, with regard to Figure 8A, I am very confused about the targeted binding of lncRNA Erbb4-IR to the 3'UTR region of pri-miR-29b. If the conclusion is tenable, then the biological process is bound to occur in the nucleus. However, Figure S7 shows that lncRNA Erbb4-IR is mainly located in the cytoplasm. The findings seem contradictory. In addition, the expression of pri-mir-29b and pre-mir-29b should be further examined to determine the role of lncRNA Erbb4-IR in the process of miR-29b production. Thirdly, miR-29b seems inappropriate in this study, since it only vaguely explains lncRNA Erbb4-IR through miR-29b regulation of renal injury in db/db mice. Does kidney-specific silencing of miR-29b really inhibit renal injury in db/db mice?

In summary, Sun *et al.* (20) clearly establish the regulatory mechanism of the novel lncRNA Erbb4-IR in the model of db/db mice, and provide a therapeutic target for DN patients. Increasingly more lncRNAs are being discovered and described with the development of RNA-seq and next generation sequencing technologies. LncRNAs are very stable in disease-related tissues, cells, and serum because of their unique structure. In addition, compared with protein detection, lncRNA extraction and detection have higher specificity, sensitivity, and stability compared with miRNAs. Thus, lncRNAs have become the new biomarkers of diagnosis and are therapeutic targets for DM. Recently, there are two notable challenges to lncRNA research. First, the lncRNA sequences need to be verified in human cells or tissues to prove whether it is functional. Second, functional lncRNAs need to be further investigated to determine if they are specifically related to one or more diseases and to explore the underlying molecular mechanisms of these associations. Consequently, there is an urgent need for further research to support clinical applications (21). Although our existing understanding of lncRNAs is just the tip of the iceberg, novel approaches and techniques will ultimately shed light on these processes and provide a new strategy for the early diagnosis, prevention, and treatment of DM.

Acknowledgments

Funding: This work was supported by the Natural Science Foundation of China (No. 81260134, 81560148), and the Student Innovation Project of Central South University (No. 2017zzts010).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Chunlin Ou, MD, PhD (Cancer Research Institute of Central South University, Changsha, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.03.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: He X, Pu C, Ou C, Zhou S. The emerging landscape of lncRNAs in diabetic nephropathy. Transl Cancer Res 2018;7(Suppl 4):S463-S465. doi: 10.21037/tcr.2018.03.07